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* This series of papers is the result of a conference on *Hypothermia* held and supported by The New York Academy of Sciences on November 13 and 14, 1958.

INTRODUCTION: ZONES AND STAGES OF HYPOTHERMIA

E. F. Adolph

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Hypothermia refers to body temperatures lower than the usual ones. In mammals and birds, the so-called warm-blooded animals, the core of the body is ordinarily at 35° C. or higher. Only when regulation of body temperature is interfered with or overpowered does the core temperature fall. While some species are known to dispense with customary regulation, as when entering a state of natural hibernation, most mammals require forced cooling in order to become hypothermic.

Artificial cooling can be inflicted quickly either by external means, as by contact with cold water, ice, or other such refrigerant; or by internal cooling, as by the extracorporeal circulation of blood through cooling coils. The former method is adequate in small animals; the latter is commonly resorted to in animals weighing more than five kilograms. Compensatory warming is often prevented by anesthesia or narcosis. Later, rewarming is aided by surface warming or by warming the coils containing the externally circulating blood. Sometimes localized warming, as of the heart region, is used.

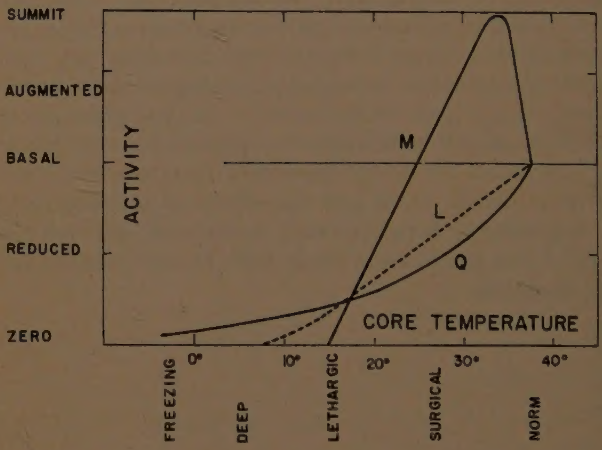

FIGURE 1. Activity ratio in relation to body temperature. Stages of activity (*ordinate*) are represented as above or below the basal that occurs in euthermia or norm. Zones of core temperature are given names (*abscissa*). Sample activities M, L, and Q are each shown in relation to hypothermia.

The task of students of hypothermia consists of measuring the changes in function that occur with body temperature. These functions, here referred to as activities, all eventually diminish in rate or intensity as temperatures decrease. However, temporarily some functions such as oxygen consumption or heat production markedly increase. Each activity may be related conveniently to the temperature of the tissue manifesting it (FIGURE 1).

Activities do not change in parallel. Hence physiological distortions result at all low body temperatures, relative to the integrated state at the usual temperatures. Upon further cooling, some activities cease; these cessations are referred to as biological zeros. Zeros occur at different temperatures for various activities; zeros help to characterize the functions.

Having designated the various stages of activity as basal, augmented, summit, reduced, and zero, we can usefully distinguish zones of body temperature at which the modifications occur (FIGURE 1). We can think of the usual body temperature as a norm, and successive zones of hypothermia as surgical, lethargic, suspended, and freezing. As we shall see, none of the zones is necessarily lethal.

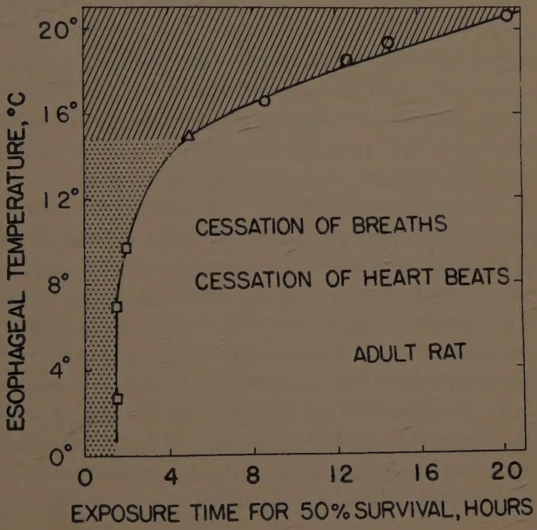

FIGURE 2. Exposure times (*abscissa*) that were survived by 50 per cent of unanesthetized rats at various body temperatures (*ordinate*). Below 15° C. artificial breathing was administered during the exposure, and was required for recovery. Darkened areas are the viable zones for exposure.

When activities have ceased at their characteristic temperatures, they usually recover upon rewarming. After a sufficient time, however, their cessation becomes irreversible. Death is characterized by the irreversibility of some essential function; but it may also be characterized by the failure of some complex or coordination. Each activity may recover within a limit of time; only when low temperatures prevail for too long a period does death result. A temperature-time contour thus defines the limits of viability (FIGURE 2). These time limits are found, however, not only near 0° C., but also at temperatures of 15° C. to 25° C. where there is no known suspension of a measurable activity.

Methods of study of hypothermic states include not only observations on intact animals and all their parts, but measurements upon separate organs and tissues *in situ*. Cold blocks and narcoses thus become tools for the study of numerous functions. Isolated tissues can be observed for continuance of activity and for survival. Various models and chemical systems may be set up for comparison with intact tissues.

Indeed, the complete hypothermist can learn valuable lessons from many phenomena in cells and tissues; energetics, mechanics, enzymes, equilibrium states, kinetics, phase shifts, electrolyte effects, electric potentials, and optical activity. He will delve into processes of movement, conduction, transmission, cell division, adaptation, regulation, protein synthesis, and growth, as well as blood flow, breathing, and other usual organ activities. Also he naturally will learn these lessons from a wide variety of organisms.

Evidently a great number of activities need to be followed at low temperature. Temperature is a dimension in the physiological constitution of a tissue, and the tissue's response reveals certain of its capacities. We have the further task of seeing how each modified activity fits a place in a total pattern of the cold organism. That pattern describes, more or less adequately, the organism that will not tolerate hypothermia indefinitely.

In my estimation, what physiologists of hypothermia need most is, first, a good theory, more comprehensive than the pioneer one of Arrhenius, as to how the concept of heat as a form of molecular energy applies in living systems; and, second, a valid theory of what kills organisms that attain various low temperatures. For mammals, we have three prominent notions about cold death: (1) destruction of some limiting process or structure, (2) stoppage of energy transformations at low temperature, and (3) disproportion among retarded processes. Each of these notions has guided a host of investigations; we now find available large bodies of detached information that have not yet crystallized our understanding of how hypothermia limits life.

VIABILITY OF SUPERCOOLED AND FROZEN MAMMALS

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On March 23, 1756 a Swedish peasant intoxicated with brandy was bowled over by the wind and fell asleep in the snow. He was found next morning frozen stiff, and was put into a coffin ready for burial. Later in the day a physician arrived unexpectedly and examined the body. The face and extremities were ice-cold, the joints immovable, the eyes fixed open, and there were no signs of breathing or heartbeat. However, the physician, S. Naucler, thought that there was some warmth at the pit of the stomach and ordered the arms and legs to be rubbed while he applied hot fomentations to the trunk. As a result, the patient gradually revived and, next day, was recovering. This case was reported fully in the proceedings of the Swedish Academy of Sciences (Naucler, 1757) and in *The Scots Magazine* of 1759.

Many similar cases have been described during the past 200 years. The best documented of these is Laufman's account of a Negro woman in Chicago who lay in a drunken stupor at an air temperature between −18° and −24° C. all night. When she was rescued the next day she was pulseless, but the heart was beating 12 to 20 times per minute and she was breathing 3 to 5 times per minute. The rectal temperature was 18° C. and, judging by the subsequent rate of rise, probably had never been below 16° C. The extremities were much colder and became so severely frostbitten that it was necessary to amputate the legs below the knees, and all the fingers and one thumb were lost. Nevertheless, she survived (Laufmann, 1951). The question is whether a high blood alcohol level favors survival from severe hypothermia, or whether the intoxicated merely are more liable to expose themselves. Thus far there is no evidence that any human being whose internal temperature has reached freezing point has recovered.

More than a century ago Bernard (1876) found that the internal body temperature of mammals could be reduced by immobilizing them in contact with chilled mercury or snow. Guinea pigs so treated recovered after the deep body temperature had reached 18° or 20° C., but at 16° C. breathing and heartbeats stopped and were not resumed when the animals were rewarmed. In 1881 Horvath recorded body temperatures as low as −0.2° C. in hibernating marmots that subsequently roused spontaneously (Horvath, 1881). Horvath did not suppose that the animals were frozen. Since then E. F. Adolph and other physiologists have established the lethal body temperatures for adult mammals of a great variety of orders and species, some of which hibernate (Burton and Edholm, 1955). In every instance the result was essentially the same: breathing and heartbeats stopped and the animals died when the internal temperature was still well above the freezing point of plasma.

The report by Bachmetiev in 1912 that hibernating bats survived cooling to body temperatures as low as −9° C. was exceptional, and his theory that animals could survive total freezing of all their body water generally was not accepted. Further studies on cooling bats have been carried out in recent years by Kalabukhov (Kalabukhov, 1934, 1958), who finds that these mammals have a remarkable capacity for becoming supercooled, both under natural and under experimental conditions, particularly when they are immature. Kalabukhov recorded deep body temperatures and electrocardiograms, and demonstrated that the heart continued to beat in bats in the supercooled state. Some of his results are shown in TABLE 1.

TABLE 1

CHANGES IN THE HEARTBEAT IN BATS (*Nyctalus leisleri*)*

State of animal	Body temperature (°C.)	Number of heartbeats per minute
Active	+37.3	420
Dormant	+ 4.1	16
Undercooled	− 4.33	8.5

* Kalabukhov, 1958.

Kalabukhov has succeeded in keeping bats in the supercooled state for several hours and even for days at temperatures between −5° and −7° C. When rewarmed, the animals regained full activity. The presumption is that the heart had continued to beat throughout the period during which the body temperature was below zero. Kalabukhov found that bats that had been frozen extensively did not recover, and emphasized that spontaneous crystallization of ice in supercooled bats was lethal. In the past, the supercooled state has been regarded as highly unstable, and it was thought that vibrations might precipitate freezing which, in any case, would sooner or later occur spontaneously. This view must be revised in the light of the discovery by Scholander and his co-workers (1957) that deep water arctic fish are permanently supercooled by about 1° C. The fish swim around actively and feed themselves throughout the year in the supercooled state, but die if they become seeded with ice crystals and freeze. Supercooled bats are, of course, torpid and their survival probably is limited to the period for which starvation is tolerated by the beating heart and the rest of the organism.

There are other examples in nature of animals that survive in the supercooled state with vital functions slowed but not arrested. I propose, however, to turn to the problem of resuscitating mammals in which the internal temperature has dropped below the freezing point and in which respiration and circulation are at a complete standstill. A few years ago all the scientific evidence suggested that such a project was hopeless. New prospects were opened by R. K. Andjus (1951), who demonstrated that about 20 per cent of adult rats could be resuscitated after 1 hour without breathing or heartbeats at body temperatures just above 0° C. Improvements in the technique of resuscitation at the National Institute for Medical Research resulted in the revival of between 75 and 100 per cent of rats and mice kept in this way. (Andjus and Smith, 1954, 1955; Andjus and Lovelock, 1955; Goldzveig and Smith, 1956*a*). Andjus also found that rats would survive supercooling to several degrees below zero, but not partial freezing, when treated by the methods then in use (Andjus, 1955). It was a particular pleasure to learn three years ago in Washington, D. C., that Niazi and Lewis, working independently and using entirely different methods had resuscitated ice-cold and inanimate rats and also monkeys that had been cooled to temperatures only a little above zero and well below the previously accepted lethal limit at which breathing and heartbeats cease. The behavior of these monkeys, in which cardiac standstill had lasted for up to two hours, apparently was not altered and no neurological abnormalities were detected in the months following reanimation (Niazi and Lewis, 1957). We found by precise psychological tests that rats that had learned to solve problems before cooling showed no significant loss of memory after resuscitation from body temperatures just above 0° C., in spite of complete suppression of spontaneous cortical electric activity for periods of up to 2 hours (Andjus *et al.*, 1955, 1956). The fertility of the rats was reduced soon after reanimation, but a few weeks later reproductive capacity was regained and many normal litters were produced and reared by parents that had been kept for 1 hour with arrested respiration and circulation at body temperatures between 15° and 0° C. (Goldzveig and Smith, 1956*b*).

Golden hamsters, artificially cooled by the method used for rats, were easier to resuscitate. Heartbeats were recorded at colonic temperatures between 2° and 6° C. By the time the internal temperature had reached 12° C. the hamsters were breathing naturally and shivering vigorously and thereafter required no further treatment. Hamsters survived longer periods of suspended animation at 0° C. than rats, and recovered fully after breathing and heartbeats had been at a standstill for 2½ hours. For these reasons hamsters were used to determine whether mammals would survive reduction of their internal body temperature to levels below the freezing point of plasma and tissue fluid (Smith *et al.*, 1954). At this point I must emphasize that, during natural hibernation, breathing and heartbeats do not stop, nor do hibernating mammals of any species studied to date become frozen, because metabolic processes and heat production continue and the animals increase the metabolic rate or else rouse spontaneously when the environmental temperature falls below zero (Lyman, 1948). The physical processes of freezing and thawing are just as unnatural and dangerous for the cells and tissues of the hamster as for those of the mouse or man or any other mammal.

In the first stage of each experiment the hamsters were cooled as before by the closed vessel technique of J. Giaja (Andjus and Smith, 1955). The animals became anesthetized by the combined effects of the falling oxygen and rising CO_2 tensions of the cold atmosphere they breathed and by the resultant fall in body temperature. They were then transferred to baths of melting ice, with the result that the body temperature fell rapidly, passing in about 30 min. from 17° C. to 2.5° C., at which temperature heartbeats, as judged by electrocardiograms, had usually ceased. The inanimate animals were then placed in baths of propylene glycol at −5° C. Within 5 or 10 min. the internal body temperature reached 0° C. and then fell below zero.

In about 25 per cent of the animals the subcutaneous and deep body temperatures continued to fall, as shown in the FIGURE 1*a*, and gradually approached the temperature of the bath which, in some experiments, was reduced from −5° to −8° C. These animals remained soft and unfrozen and were, obviously, in the supercooled state with body temperatures well below the freezing point of plasma. Supercooled hamsters with internal temperatures as low as −5° C. were resuscitated completely by heating the entire body with diathermy or under bench lamps while artificial respiration was given (Smith *et al.*, 1954).

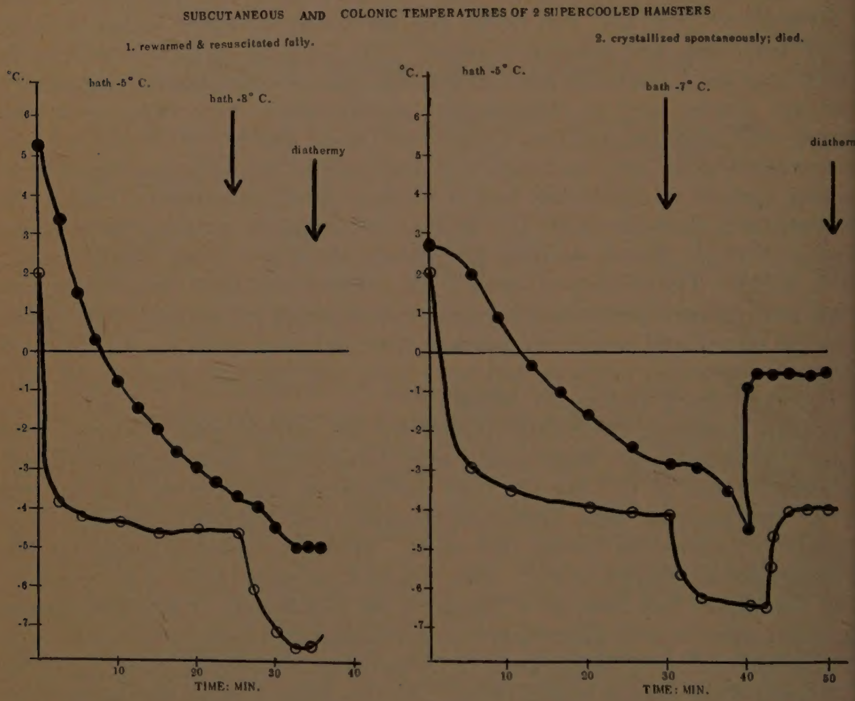

FIGURE 1

In some of the supercooled hamsters that apparently had been cooled in exactly the same way, the deep body temperature rose suddenly to a level at about −0.6° C. and soon after the subcutaneous temperature rose to about −2° C. while they were still immersed in fluid at −5° to −8° C. (FIGURE 1*b*). The only possible explanation for this rise in temperature was that freezing had occurred spontaneously and that evolution of latent heat of crystallization had warmed the interior of the body. This explanation was supported by the progressive stiffening of the body which subsequently occurred while its internal body temperature remained at the freezing point of plasma (Smith *et al.*, 1954). When resuscitation was attempted immediately after the onset of crystallization, as judged by the rise of colonic temperature, hamsters that previously had been supercooled to internal temperatures as low as −3.0° C. usually recovered fully, whereas those that had been supercooled to deep body temperatures of between −3.0° and −6.0° C. succumbed, although heartbeats and natural breathing were restored temporarily in some instances. When resuscitation was delayed until the previously supercooled animals had been freezing for 10 to 30 min., they seldom showed any signs of revival (Smith, 1956*b*).

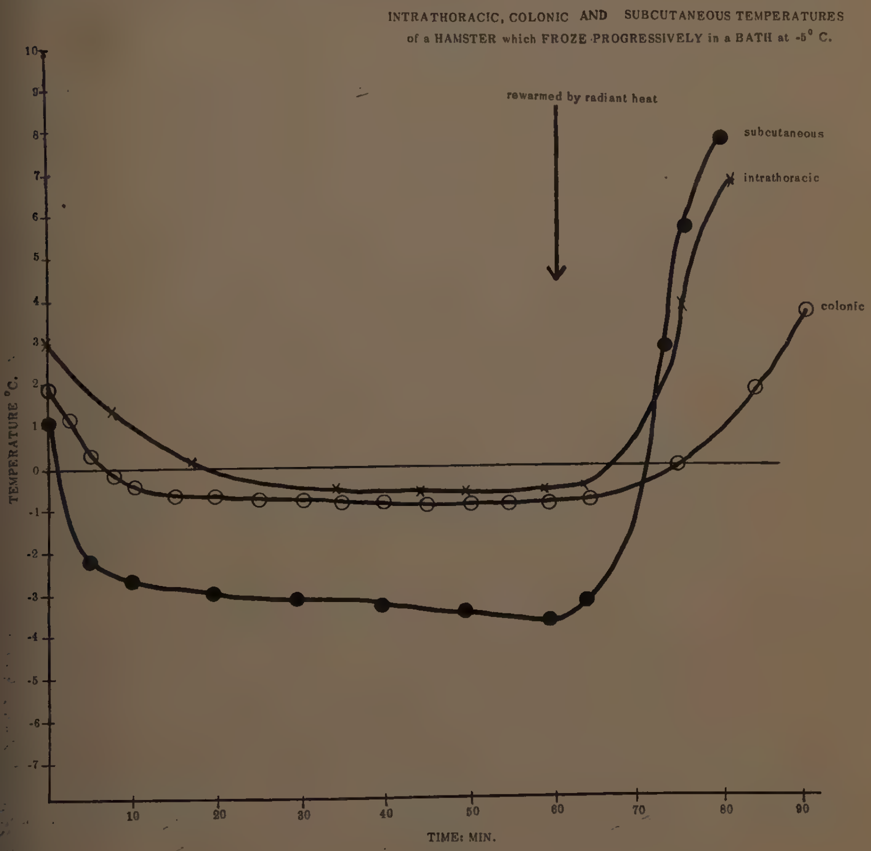

FIGURE 2

By contrast, about 75 per cent of the hamsters began to freeze soon after immersion in the bath at −5° C. The ears and paws began to stiffen perceptibly before the deep body temperature had reached zero. Gradually during the next 30 to 60 min. the whole surface of the animal became rigid while the colonic temperature remained at a level between −0.5° and −0.9° C., as shown in FIGURE 2 (Smith *et al.*, 1954). The intrathoracic and cerebral temperatures reached about the same level, but the subcutaneous temperature fell to between −2.5° and −4.5° C., depending upon the position of the thermocouples (Smith, 1956*a*). Saline and serum froze within capillary tubes that had been inserted into different parts of the body and ice crystals could be seen in the subcutaneous tissues, in the abdominal and thoracic organs, and in the brains of animals that were dissected in the frozen state. Calorimetric determinations showed that after one hour in the bath at −5° C., 40 to 50 per cent of the body water had been converted into ice (Lovelock and Smith, 1956). Nevertheless, a high proportion of hamsters frozen progressively for 40 to 60 min. recovered fully after thawing with diathermy and the administration of artificial respiration. The extremities were not frostbitten unless they had been bent in the frozen state (Smith, 1954, 1956*b*). Although the surface of the body was undamaged, most of the frozen hamsters passed fresh blood per rectum during the first few hours following reanimation and autopsies showed that the site of bleeding was the stomach. A few animals died several weeks later with perforated gastric ulcers. When pregnant hamsters were frozen on the ninth, tenth, or eleventh day of the 16-day gestation period, placental hemorrhages occurred, and many of the fetuses were resorbed. Hamsters frozen for short periods at other stages of pregnancy delivered and reared normal young. However, grossly deformed fetuses were found in some of those frozen for 45 to 60 minutes (Smith, 1957*a*).

I mention these findings partly because of their intrinsic interest for pathologists and embryologists and partly to correct the impression that freezing the whole animal can be regarded as an innocuous process. Even a small rodent as sturdy as the hamster depends greatly on the recuperative powers of the body to repair the damage that occurs while circulation is at a standstill and when water is withdrawn from the blood and tissues by the formation of ice. The hazards of severe hypothermia and of freezing and the need for fundamental studies of the damage to individual organs as well as to the animal as a whole were more obvious when an attempt was made to repeat the experiments on larger mammals (Smith, 1957*b*).

When rabbits 1 to 2 kg. in weight were enclosed in vessels 10 to 20 liters in capacity in a cold room at −2° C. they became comatose after about 3½ hours. The deep body temperature at this stage was 30 to 32° C. The animal recovered after taking several breaths of fresh air and resisted immersion in icy water. Induction of hypothermia was hastened by admitting 3 liters of CO_2 to the box enclosing the rabbits and allowing a corresponding amount of air to escape. Three hours later the respiratory rate was 40/min., and the animals remained comatose after admission of 1 to 2 liters of oxygen. Thirty minutes later the deep body temperature was between 23° and 18° C., and no responses other than the corneal reflexes could be elicited. Rabbits so treated recovered spontaneously in air at +20° C. Others, transferred to icy water, continued to cool very slowly and were still breathing 30 min. later with colonic temperatures between 20° and 14° C. Three animals dried at this stage recovered at room temperature, but one died the next day and another within a week. Rabbits left in melting ice stopped breathing at body temperatures between 18° and 12.0° C. Heartbeats and natural breathing usually could be restored temporarily by rewarming under a radiant heat lamp and giving artificial respiration, but of 6 rabbits kept with breathing and circulation arrested for 20 to 40 min., at body temperatures between 12° and 9° C., only one recovered fully and it died 3 days later. At autopsy the conspicuous abnormality in each instance was a massive gastric hemorrhage.

It seemed possible that less damage would occur after respiratory and circulatory arrest if the interior of the body could be cooled rapidly to a lower temperature and that more efficient methods of rewarming and giving artificial respiration would be needed. The problems involved are dealt with in detail by J. E. Lovelock elsewhere in this monograph. The rate of cooling was increased greatly when the stomach and intestines were irrigated with an ice cream mixture and when the rabbits had been completely depilated, but the gastric and intestinal lesions were intensified and there seemed little prospect of restoring to good health rabbits without any fur. When the abdomen had been shaved and the rest of the fur washed with detergent, the rectal temperature of rabbits immersed in vigorously stirred baths at −5° C. fell from +18° C. to −0.5° C. within one hour of cessation of breathing and heartbeats. By this time the extremities and superficial tissues had been freezing for about 45 min. and the subcutaneous temperature was about −2.5° C. The quantity of ice formed and the energy needed to thaw them was, therefore, much greater than had been required for the hamsters. In early experiments in which diathermy was used, both dielectric and induction heating tended to burn the surface tissues without warming the interior organs of the rabbits. Modifications of technique resulted, at first, in cooking the internal organs. Eventually these hazards were overcome and the frozen rabbits were thawed within a few seconds and the deep body temperature was raised from 0° to +10° or +15° C. in 1 min. The energy input was then reduced so that the colonic temperature rose by 1° to 2° C./min. while cold air was blown over the surface of the body. Fifteen frozen rabbits were treated in this way. In each instance the heart resumed beating when the colonic temperature was about 15° C. and the animals breathed spontaneously at colonic temperatures between 20° and 30° C. They regained corneal reflexes and made spontaneous movements, but collapsed and died within an hour whether or not warming was continued. Autopsies showed that there had been massive hemorrhage from the fundus of the stomach. Microscopic studies showed that bleeding was restricted to regions in which oxyntic cells were present. The pyloric part of the stomach was normal. A similar hemorrhagic lesion occurs in rabbits at normal body temperatures after injections of posterior pituitary extracts (Dodds *et al.*, 1937; Cutting *et al.*, 1937). It is due to intense gastric vasoconstriction and the resultant reduction in volume and increase in acidity of the gastric juice secreted. It can be prevented by neutralizing the gastric contents. We realized that, when circulation was arrested by severe hypothermia, hydrochloric acid would diffuse from the lumen into the wall of the stomach and would erode the blood vessels, just as it does after administration of posterior pituitary hormones, and that bleeding would be inevitable when circulation was restored unless the hydrochloric acid had been neutralized. Rabbits were therefore muzzled to prevent coprophagy and starved for 18 hours so that the stomach would be empty when cooling was started. Thirty cc. of a saturated solution of sodium bicarbonate was introduced into the stomach before the hypothermic animals were immersed in the bath at −5° C. Four rabbits treated in this way were frozen and resuscitated as before. Survival was definitely prolonged, but all the animals died within 4 hours of resuscitation despite the fact that gastric hemorrhage had been prevented (Smith, 1957).

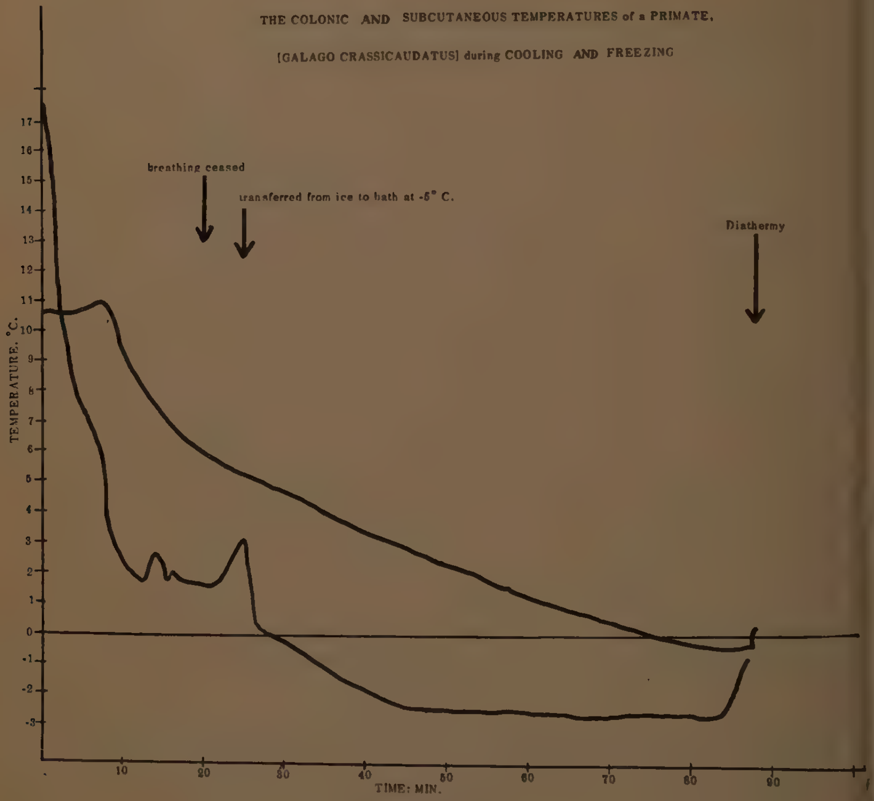

FIGURE 3

These results indicated that, in contrast to hamsters, rabbits show little capacity for spontaneous recuperation either after freezing or after comparatively slight reduction in body temperature. Some of the lemurs, on the other hand, become hypothermic under natural conditions, and temperatures as low as 18.5° C. have been recorded from healthy animals of the species *Cheirogaleus major* and *Cheirogaleus medius* (Bourliere and Petter-

Rousseau, 1953). We had been studying 6 small primates of a related species, *Galago crassicaudatus*, but had not recorded rectal temperatures below 35° C. during the day. Two of these animals cooled by the closed-vessel technique and then immersed in icy water continued to breathe until the colonic temperature reached 6.0° C., and recovered when rewarmed either at that stage or after respiration had ceased for 20 min., and from a deep body temperature of 4° C. Two galagos were then cooled and rewarmed by the method used for rabbits (FIGURE 3). They made a good initial recovery after freezing for 40 min., at body temperatures below 0° C., but died within an hour; in each instance the stomach contained fresh blood. Two galagos were then treated by running 10 cc. of 4 per cent sodium bicarbonate into the stomach before freezing. They resumed natural breathing and then died. At autopsy the bronchioles contained large quantities of frothy fluid with an alkaline reaction and it was clear that, at some stage, the animals had regurgitated and inhaled the sodium bicarbonate. In the remaining 2 animals a tracheotomy tube was inserted and left in place until they had recovered muscle tone and spontaneous movements as well as natural breathing. These 2 galagos made an excellent initial recovery, but died within 24 hours. At post-mortem the lungs were edematous, and blood-stained fluid could be expressed from them, but this might have been secondary to cardiac failure (Smith, 1957). Death may have resulted from some physiological or physicochemical disturbance that could be counteracted by altering the methods of cooling and resuscitation and by instituting some form of aftertreatment. The number of experiments was small, but the results, although disappointing in their final outcome, suggest that non-hibernating mammals larger than the hamster and as high in the evolutionary scale as the primates are not killed by short periods of freezing at temperatures close to zero. In the future it may well be possible to restore them to full health. Meanwhile, information is being collected about the behavior of individual organs and systems to which circulation is restored after freezing and thawing.

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PHYSIOLOGY OF DEEP HYPOTHERMIA BY TOTAL BODY PERFUSION

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It is my conviction that hypothermia of 0° C. is compatible with life of adult, large, nonhibernating mammals if adequate perfusion of the vital organs is maintained. The intact heart of peripherally cooled adult dogs breathing air or oxygen goes into ventricular fibrillation or stops beating between 19 and 26° C. If ventricular fibrillation is prevented by a slow intravenous drip of diluted quinidine (30 mg./kg.), the temperature of dogs can be reduced further to about 12° C. while some blood is still circulating (FIGURE 1). The euphoria of investigators who have taken this hurdle soon changes into despondency when they try to rewarm the animals. Except for animals under the Giaja effect of general vasodilation by hypercapnia,[1] all

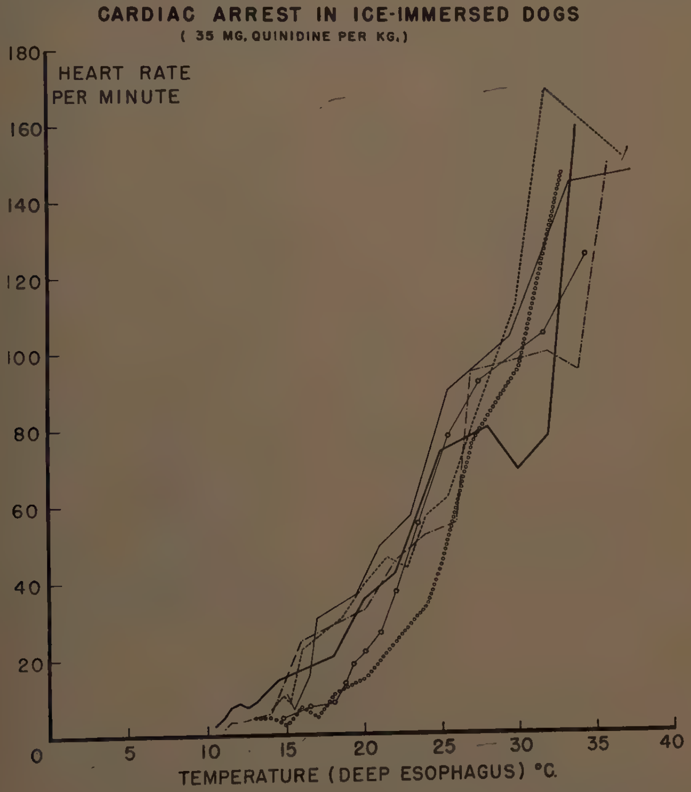

FIGURE 1. Prevention of ventricular fibrillation by slow intravenous drip of diluted quinidine (35 mg./kg.) in dogs cooled to cardiac arrest by immersion in ice water.

attempts at survival have failed so far because research enters a dead-end street; in order to start the circulation of blood, it is necessary to raise the temperature and, in order to raise the temperature, circulation of blood is required. This vicious circle does not lead to the vital circulation. At this point of impending catastrophe the necessity of an artificial circulation becomes evident and a pump-oxygenator appears like a *deus ex machina*. What was first a technical convenience of a small and simple instrument to cover the reduced oxygen consumption[2] later changed into a new concept of tolerance to cold when systematic investigations unearthed new phenomena.

Extracorporeal cooling is not new. At the beginning of World War II Heymans at the University of Ghent, Ghent, Belgium, constructed a glass cannula with a water jacket that enabled him to cool and warm the blood in a carotidojugular shunt in more than 300 rabbits.[3] By directing the flow of blood up or down the jugular vein, he induced pronounced temperature changes in the brain or in the heart; a thorough study of hemodynamic and respiratory functions enabled him to explore the brain damage above 43° C. and the cardiac crisis below 18° C. These experiments were conducted under the extreme conditions of war and occupation and Heymans' dedication to science and freedom should be honored by linking his name inseparably to blood cooling. Since then many investigators have used arterial and venous blood cooling for experimental and clinical purposes. However, as long as one was forced to rely on the hypothermic heart of the animal or patient to provide adequate perfusion, the procedure still encompassed the limitations of surface cooling. Only by making the circulation and oxygenation of blood independent of the hemodynamic changes of induced hypothermia[4] has the barrier to the rate, degree, and duration of cooling of large animals been removed.[5]

During the last decade the method of total body perfusion has been perfected to such a degree that problems today are not technical, but physiological in nature. Any of the available pump-oxygenators can be adjusted to cool and rewarm the circulating blood and, for reasons of simplicity only, an instrument was designed that combines the pumping, oxygenating, and thermoregulation of blood in one chamber (FIGURE 2). The gas exchange is based on the bubble-defoam principle;[6] the circulation of blood is accomplished by photoelectric cells energizing alternately magnetic valves leading to pressure and suction lines;[7] and the temperature of the blood is changed by the insertion of a coil into the instrument. Dogs are pretreated with 500,000 U. penicillin, 50 mg. promethazine hydrochloride, 30 mg. quinidine/kg., 5 mg. heparin/kg., and small amounts of a fast-acting barbiturate, as needed. They are kept intact except for a small skin incision in the inguinal region to withdraw venous blood through a multiple perforated catheter in a femoral vein advanced into the right atrium and to return the oxygenated blood through a catheter in a femoral artery advanced into the descending aorta.

The temperature differences within the body produced by cooling blood with a pump-oxygenator can be made more pronounced[8] and selective since the flow rate does not depend on the animal's own heart. By shunting only part of the venous return into the instrument and by returning the cold, oxygenated blood into the arch of the aorta, the viscera of the upper part of the body can be cooled to or almost to 0° C. within one hour, whereas the temperature changes of skin, subcutaneous tissue, and muscle are less marked (FIGURE 3). The same temperature gradients prevail on rewarming. Thus, cooling with a pump-oxygenator rapidly lowers the oxygen consumption of the vital internal organs by perfusing them with oxygenated blood, whereas cooling by ice immersion rapidly lowers the oxygen consumption of the less vital periphery. The difference between these two methods becomes of far greater importance during rewarming. During peripheral rewarming the highly increased oxygen demand of the skin, subcutaneous tissue and the muscles, or of the major part of body weight, cannot be met by the still decreased output of the too cold heart. Rewarming with a pump-oxygenator rapidly raises the oxygen consumption of the heart and the internal organs by simultaneously and proportionately covering their increased demand with sufficient oxygen. This results first in an increased cardiac output, which then rewarms and oxygenates the less vital periphery.

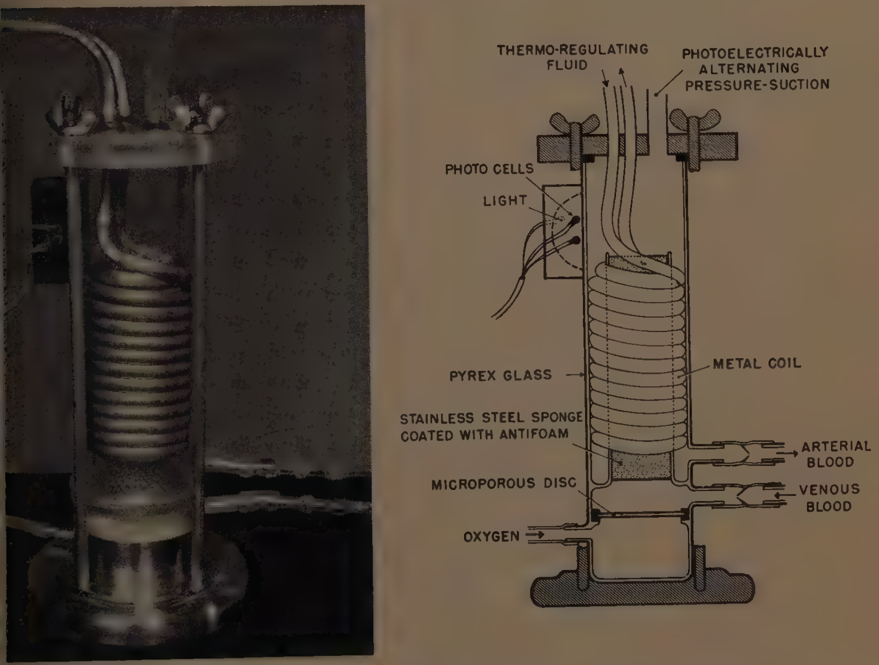

FIGURE 2. Single-chamber pump-oxygenator and thermoregulator.

The use of a pump-oxygenator for the production of hypothermia extends the study of an isolated perfused organ to the study of a perfused organism. When Langendorff[9] perfused isolated cat hearts from an elevated reservoir in 1895, his first application of this new technique was the study of the temperature effect. It is fortunate for us that 60 years ago medical scientists did not think it fashionable to have a biostatistician decide whether their work was due to chance or statistically significant but biologically insignificant; therefore we derive great benefit from the published protocols of Langendorff's experiments. This investigator noticed that as the temperature fell the rate of the heart decreased, first with greater speed than later at lower temperature; therefore, not a straight line, but a curve resulted. It did not worry him that the complex function of an entire organ did not follow van't Hoff's rule of simple chemical reactions, but he pointed out that the temperature-heart rate curve of the perfused mammalian heart resembled closely the same relationship in the amphibian heart. In experiment No. 4, he recorded that a perfused cat heart stopped beating at 6° C. The hearts of dogs I used behaved the same way during total body perfusion (FIGURE 4). There is considerable variability from dog to dog, but spontaneous contractions can always be recorded below 10° C., and some hearts continue to beat at 2° C. When Langendorff's isolated hearts stopped beating above

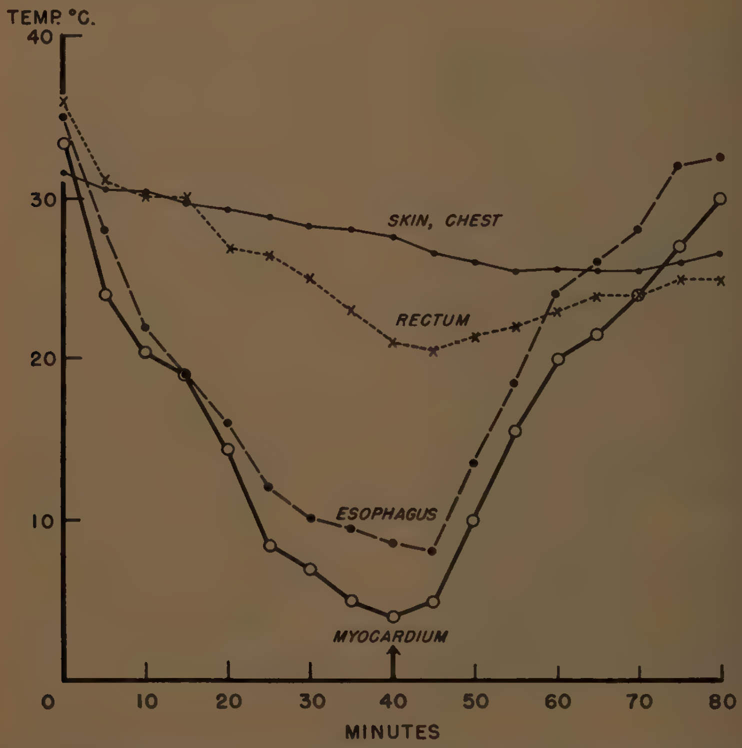

FIGURE 3. Temperature gradients between internal organs and periphery produced by the return of oxygenated, cooled blood into the descending aorta during partial cardiopulmonary bypass.

10° C. he observed: "It is evident that at even lower temperatures the heart muscle has not lost its excitability but that mechanical stimulations will be followed by very slow and weak, but still very distinct contractions of the ventricle. Even after very prolonged cooling such hearts will start to beat again if the temperature of the perfusate is raised again." It is superfluous to add a single word to describe the excitability to mechanical stimulation and the viability of dog hearts during total body perfusion. He continued,

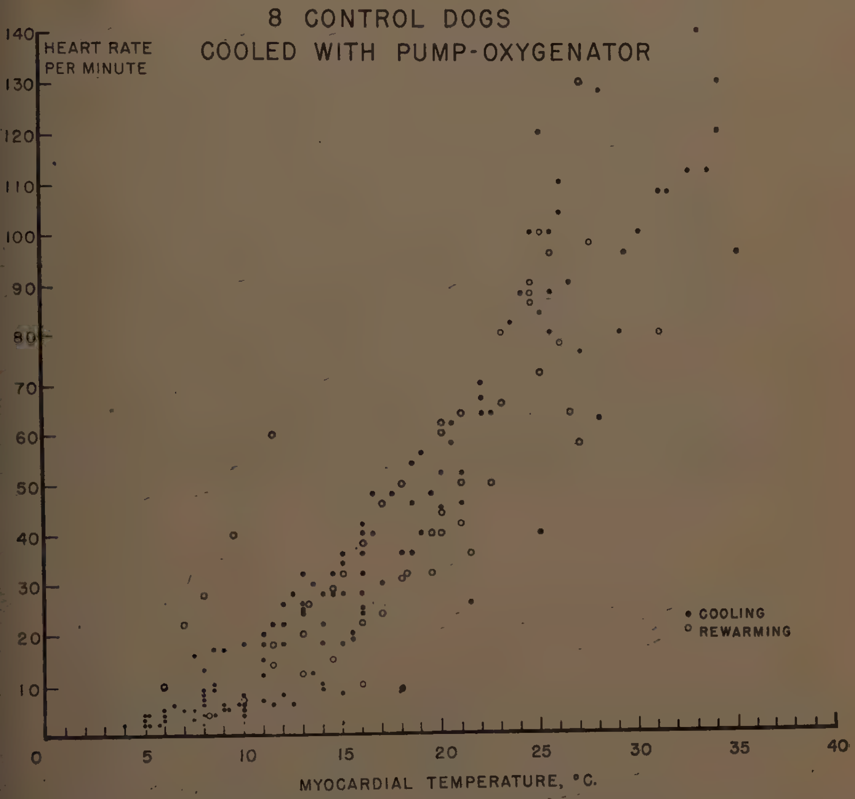

FIGURE 4. Temperature-heart rate curve of dogs cooled by body perfusion with blood equilibrated with 95 per cent oxygen.

"At times it is possible to observe arrhythmias of the heart as one passes through a zone of about 20° C. and these arrhythmias disappear as the temperature is lowered." In perfused dogs the zone of temporary arrhythmias lies at about 15° C., but in many animals no electrocardiographic abnormalities can be observed.[10] "One has to be very careful with the rewarming since the heart will easily develop ventricular fibrillation"; in perfused dogs, it is advisable to raise the temperature slowly until the heart reaches about 20° C. When the lowest temperatures are reached, slow oscillatory movements of the muscle sometimes can be seen during the long intervals between contractions (FIGURE 5 at 11° C.). "Ventricular fibrillation in cooled hearts reminds one more of a kind of peristaltic movement very similar to the ones observed in the frog heart"; in perfused dogs, it appears as if exceedingly slow sinus rhythm and ventricular fibrillation could coexist. As the myocardial temperature falls, the left ventricular pressure becomes biphasic and, later on, up to five waves (FIGURE 5*a*, *b*, *c*) can be recorded. These waves follow the strokes of the pump and may be caused by an increasing dilatation of the aortic ostium resulting in a functional aortic insufficiency.

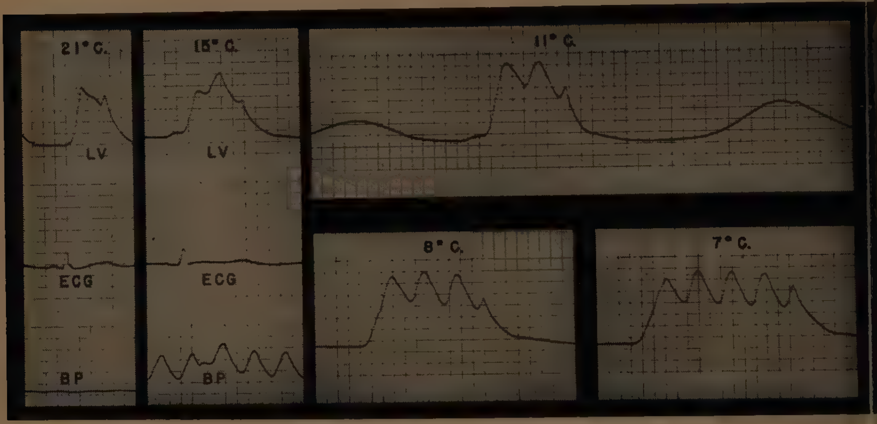

FIGURE 5. Left ventricular pressure curves during deep hypothermia under excessive perfusion pressure.

In 1896 Nawrocki, a student of Langendorff at the University of Rostock, Rostock, Germany, wrote an inaugural dissertation[11] in which he observed that as the temperature fell the amplitude of contractions of the isolated perfused heart first increased, that the greatest height was reached at about 20° C., and that from then on the amplitude of contractions decreased again. In the perfused dog the validity of this early observation can be confirmed easily (FIGURE 6) and, with the greater sensitivity of contemporary recording devices, one can show a rise of the end diastolic ventricular pressure whenever the amplitude decreases. Thus, above and below 20° C. there exists a slight degree of myocardial weakness. Above 20° C. the heart contracts with sufficient frequency to eject the coronary and thebesian flow from the right and the bronchial artery and thebesian flow from the left side. However, below 15° C., high flow rates and perfusion pressure should be avoided because they may cause dilatation and irreparable myocardial damage. I shall never understand why it took me two years and the sacrifice of hundreds of dogs to find out the simple fact that at very low temperatures "large increases in perfusion pressure are dangerous," as Langendorff puts it.

If the perfusion pressure is kept constant, a gradual decrease of coronary flow occurs (FIGURE 6) that may be due to increased intramural pressure of he cold, well-oxygenated myocardium on constricted coronary arteries. t is evident that, under controlled conditions of body perfusion, temperature irectly influences heart rate, amplitude of contraction, coronary flow, and ayocardial consumption.

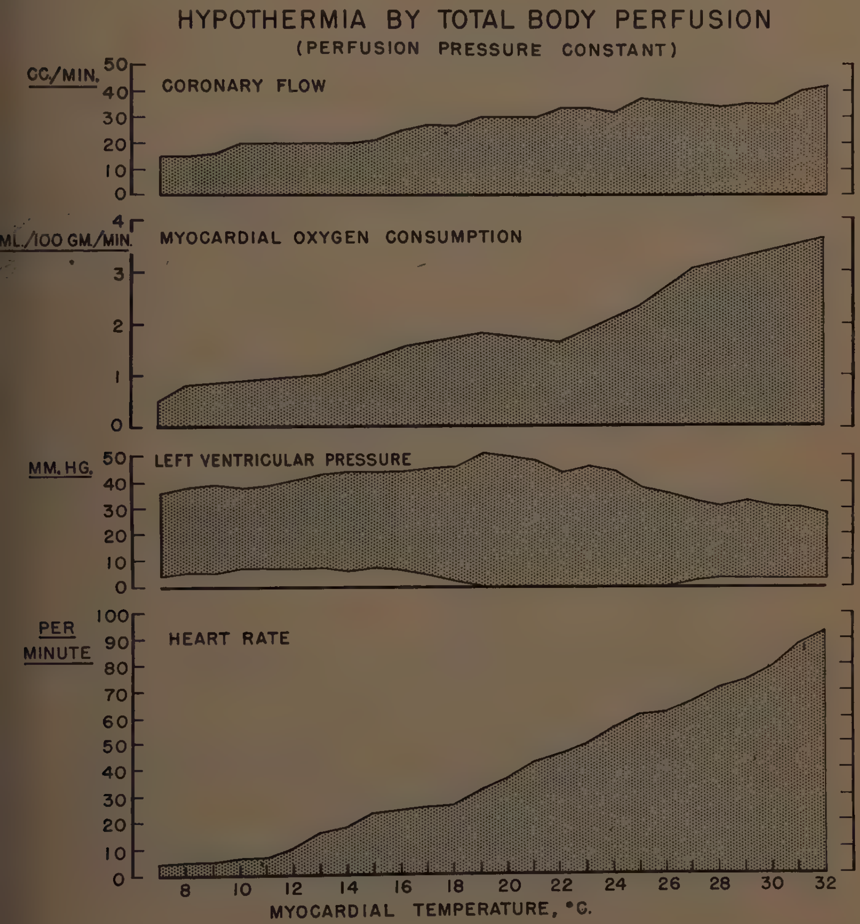

FIGURE 6. Changes of coronary flow, myocardial oxygen consumption, left ventricular ressure, and heart rate during cooling by body perfusion under constant pressure.

If the temperature is kept constant and the perfusion pressure reduced FIGURE 7), coronary flow, amplitude of contraction, and heart rate are liminished proportionately but, as a marked degree of anoxia develops, a ather abrupt fall in heart rate and rise in coronary flow[12] occur. If the erfusion pressure is raised again, the hypotonic myocardium permits the assage of a huge inflow of coronary blood. Thus, at a given temperature, he amplitude of contraction is the most sensitive and reliable criterion of dequate myocardial perfusion.

In another type of experiment one can keep temperature as well as perfusion pressure constant and change only the oxygen tension of the circulatin blood (FIGURE 8). At 23° C. and a perfusion pressure of 50 mm. Hg, substituting room air for 95 per cent oxygen, or a drop of about 400 mm. Hg tension, does not result in any reduction of heart rate, coronary flow, or lef

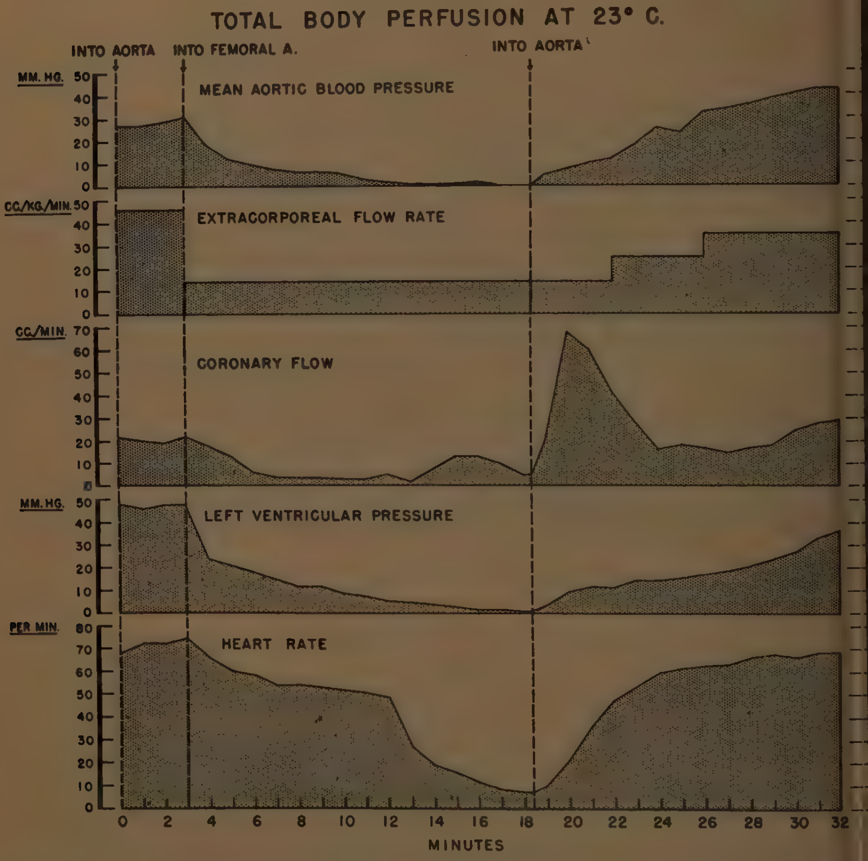

FIGURE 7. Changes of coronary flow, left ventricular pressure, and heart rate at constant myocardial temperature due to changes in perfusion pressure.

ventricular pressure. Reducing the oxygen tension of the blood graduall from 150 mm. Hg of room air to only 5 mm. Hg of commercial nitrogen i followed by a marked drop in heart rate and rise in coronary flow, but th left ventricular contractions remain much more forceful than expected This indicates that adequate coronary perfusion permits the heart to extract even minute amounts of oxygen and to maintain a considerable left ventricular pressure. When the high perfusion rate with nitrogen-equilibrated bloo at 23° C. was continued, it took 1 hour before left ventricular systolic pressur

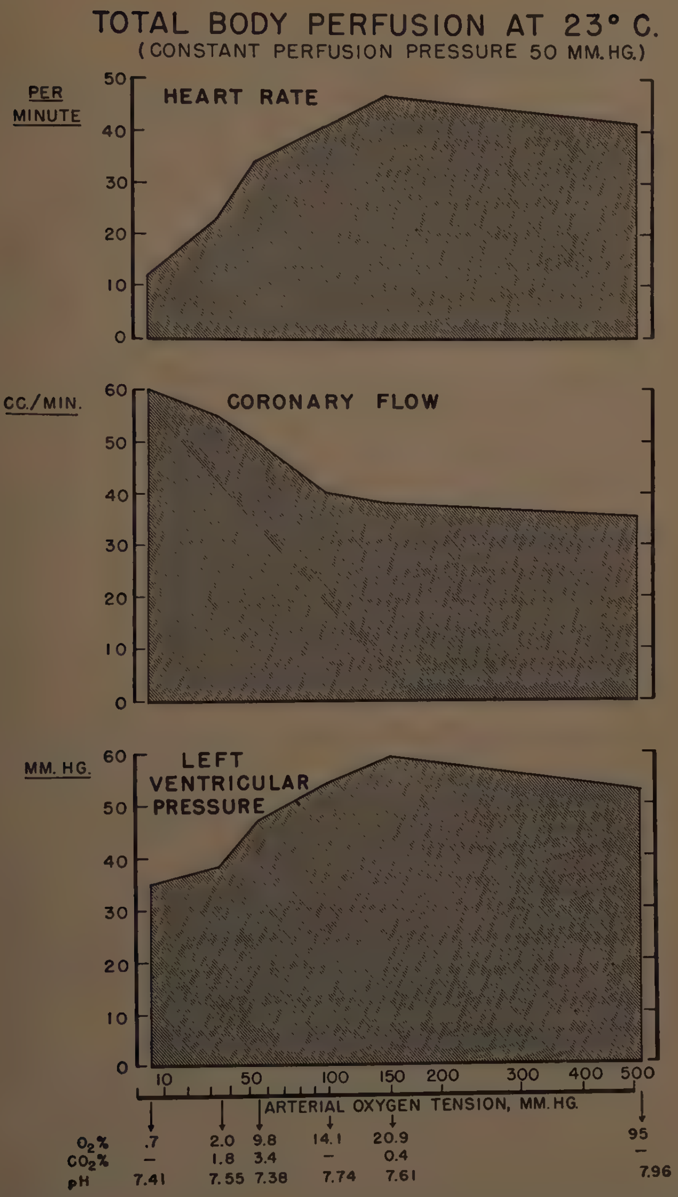

Figure 8. Changes of heart rate, coronary flow, and left ventricular pressure at constant myocardial temperature and perfusion pressure, due to changes in arterial oxygen ension.

disappeared and the heart dilated completely. At no time were arrhythmia or ventricular fibrillation observed. The paramount importance of adequat capillary perfusion of the myocardium is illustrated by the fact that a drop of only 10 mm. Hg of perfusion pressure with blood equilibrated with 95 pe cent oxygen is accompanied by a fall in left ventricular pressure correspondin to a change of oxygen tension from room air to nitrogen under constant an

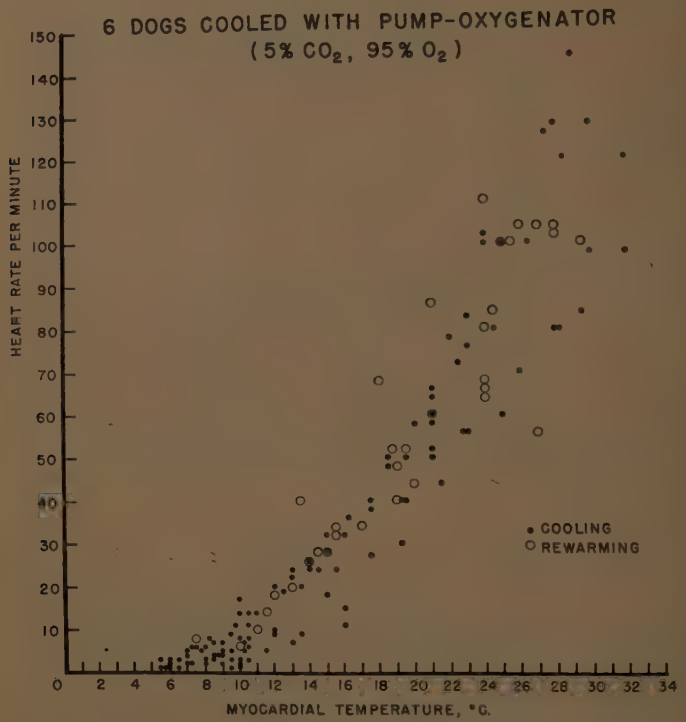

FIGURE 9. Temperature-heart rate curve of dogs cooled by body perfusion with bloo equilibrated with 5 per cent CO_2 and 95 per cent O_2.

high perfusion pressure. This remarkable resistance of the perfused hypothermic heart to deoxygenated blood explains the survival of dogs whos blood has been replaced temporarily by plasma.[13]

The gas mixtures used for the equilibration of blood contained varyin amounts of carbon dioxide and, accordingly, the *p*H underwent considerabl changes. Under the controlled conditions of such a perfusion experimen carbon dioxide and *p*H are without effect on heart rate, coronary flow, an amplitude of contractions, whereas the amount of oxygen made availabl to the heart muscle is the only factor determining its function. Therefor there is no difference in the heart rate-temperature curve between dogs coole by oxygenated blood with (FIGURE 9) or without (FIGURE 4) carbon dioxide

With an oxygen consumption of only about one tenth of normal[14] and a lmost normal supply of oxygen from the instrument, the arteriovenous ifferences in oxygen and carbon dioxide content can be made to disappear; therwise an animal without any venous blood is used. The venous oxygen ension then rises above the arterial oxygen tension of a person breathing oom air[15] and, although such a condition of extreme overoxygenation is ighly unphysiological, no deleterious effects have been observed in the

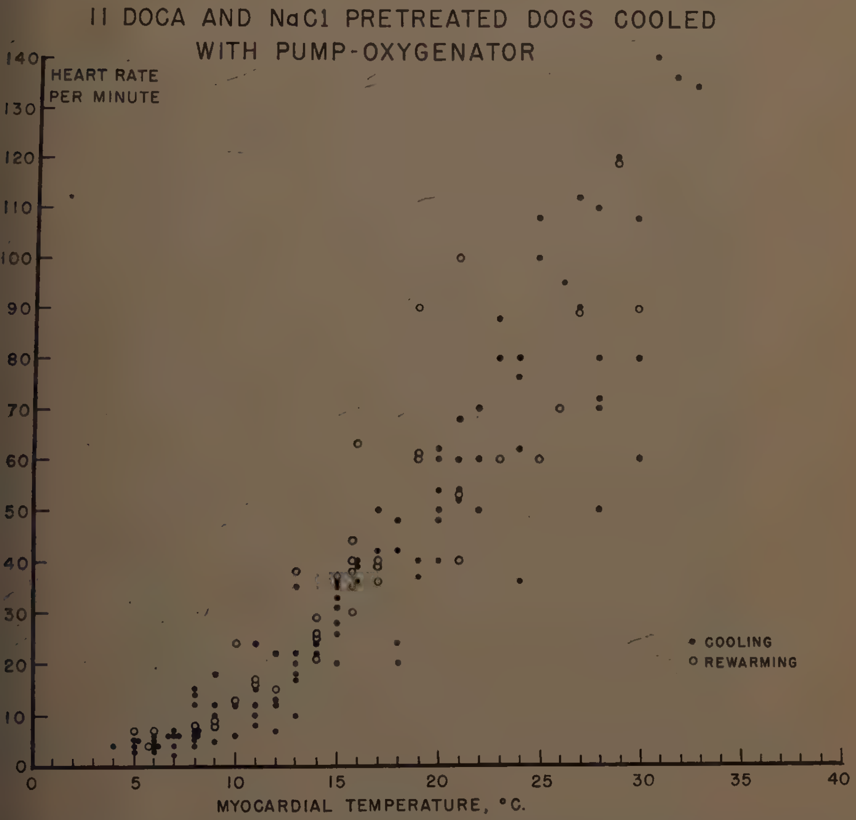

FIGURE 10. Temperature-heart rate curve of dogs cooled by body perfusion with blood quilibrated with 95 per cent oxygen. Dogs were pretreated with 50 mg. desoxycorti-osterone acetate and 10 gm. NaCl daily for a week.

urviving animals. Similarly, fears that the rewarming of ice-cold blood f high oxygen tension may cause gas embolization have not materialized, nd it appears as if the absorption of the gas by the rewarming tissues may e faster than its evolution in the blood.

The observed absence of a carbon dioxide and *p*H effect on the cardiac unction of perfused dogs at low temperature removes the importance of lectrolyte changes from serious consideration. Indeed, raising the calcium oncentration of the perfusate to 1.8 mEq., the sodium to 350 mEq., or lowering the potassium to 1 mEq. does not influence the performance of the heart. Such changes would have to be more drastic to confirm Martin's observation[16] of increased automaticity of a turtle heart at the lowest temperatures obtainable if potassium-free Ringer's solution was used as a perfusate. To exclude the possibility of a chronic effect of sodium retention, dogs were pretreated with 50 mg. desoxycorticosterone acetate and 10 gm. of NaCl daily for a week, but their temperature-heart rate curve (FIGURE 10) did not differ from that of the untreated controls (FIGURE 4).

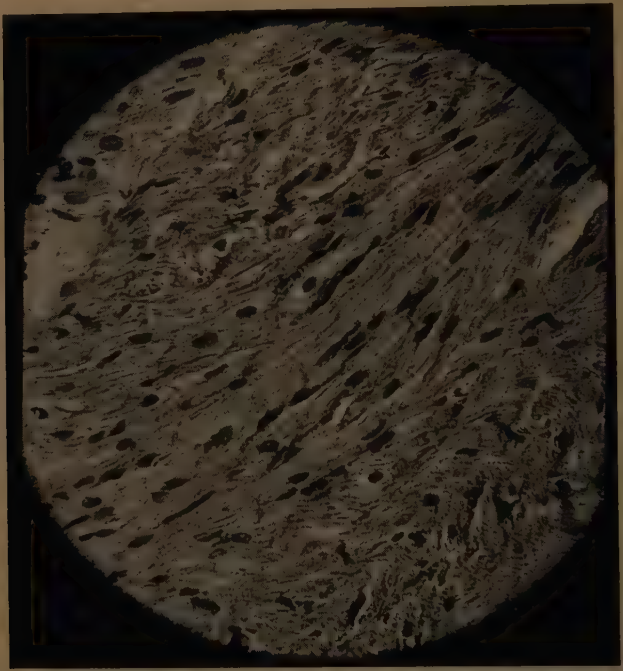

FIGURE 11. Normal myocardium after deep hypothermia by body perfusion.

"Marked vascular stasis with complete cessation of flow in some arterioles and veins as large as 60 μ in diameter" during surface cooling, as described by Bigelow,[17] has been photographed[18] and quantitated.[19] It is highly probable that the cessation of flow in capillaries causes the generalized interstitial edema,[20] fatty infiltration, depletion of glycogen, and vacuolization of cells,[21] as well as small necrotic foci in the myocardium[22] at temperatures considered optimal for cardiac operations. My colleague Raymond O Christensen, Veterans Administration Hospital, Nashville, Tenn., has done a thorough histological study of the internal organs of dogs cooled by body perfusion to 15° C. for half an hour, rewarmed, and sacrificed two days later. No pathological changes were found (FIGURE 11) that resemble those seen after surface cooling.

Conclusions

The technique of total body perfusion with a pump-oxygenator makes it ossible to study induced hypothermia under controlled conditions since emperature, perfusion pressure, rate of flow, gas equilibration, *p*H, electrolyte content, corpuscular elements, and viscosity of the perfusate can be hanged at will. Of all the factors studied, adequate and constant perfusion f the vital organs with oxygenated blood is the *conditio sine qua non* for urvival of dogs after cooling to and rewarming from 0° C. Except for a ufficient supply of oxygen to the cells at all times, all other factors are of econdary importance. The fact that total body perfusion can maintain the xcitability of dog hearts at temperatures close to the freezing point of water ndicates that the differences between hibernators and nonhibernators and etween infant and adult mammals may be caused by differences in capillary erfusion. Only the mechanism resulting in adequate capillary perfusion, ncluding cardiac output, blood volume, blood viscosity, and peripheral esistance, may vary in various species and age groups.

For reasons of convenience, I primed the oxygenator with blood diluted ith Ringer's solution and assumed that the lowered blood viscosity contributed to the survival of animals. However, perfusions with whole blood nd with severely polycythemic blood convinced me that high viscosity per se s not an essential factor. It is probable that capillary perfusion with the oncentrated blood was not as good as with the diluted blood, but was still ufficient to keep the heart beating below 10° C. A similar condition exists n hibernating animals, in whom, despite increased blood viscosity, the eating heart at 5° C. keeps a sufficient number of capillaries open[19] to guarantee survival.

Thus, all attempts to achieve a more fascinating and sophisticated explanation of the resuscitation of dogs from deep hypothermia by bringing in ormones, electrolytes, carbon dioxide, and viscosity have failed. There is o need for a new concept or a new substance, but rather the continuation f Cesalpino's circulation of blood[23] delivering Priestley's oxygen[24] to the ells. It is ironic that it took an artificial heart and lung to prove such atural truth, but there is consolation in Shakespeare's words: "This in an rt which does mend nature,—change it rather: but the art itself is nature."[25]

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LETHAL HYPOTHERMIC TEMPERATURES FOR DOG AND MAN

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Despite the considerable recent expansion in the study of the physiological ffects of hypothermia during the past two decades, beginning with Fay's[1] pplication of generalized hypothermia for therapeutic purposes, we are still ithout exact knowledge concerning either the mean lethal temperature or he exact nature of death in accidental exposure either to cold water or very old air. Reasonably exact information is available only for the anesthetized og subjected to cold-water immersion. The paucity of data on man is not ue to lack of material upon which measurements could be made so much s to the fact that the appropriate thermometer was not in the hands of nough appropriate individuals at a time when it could be applied usefully or the purpose. The same may be said for the electrocardiograph machine.

TABLE 1
COMPARISON OF TERMINAL TEMPERATURES AND TERMINAL CARDIAC EVENT IN HYPOTHERMIC DOGS UNDER DIFFERENT ANESTHETICS

	Pentobarbital	Ether	Pentothal
Number of dogs	19	10	21
Terminal heart temperature (°C.)	19.6	17.4	17.2
Number fibrillating	16/19 (84%)	7/10 (70%)	12/21 (57%)
Asystolic deaths	3/19 (16%)	3/10 (30%)	9/21 (43%)

This paper, therefore, constitutes an attempt to evaluate the meager vailable data that bear upon these questions. For the purpose, the subject circumscribed to include data on dogs and man suffering accidental hypoermia, or such laboratory-induced varieties as most closely approximate e accidental. It is limited further to acute forms, induced predominantly y cold-water immersion. Justification for inclusion of the laboratoryduced form is, as has been stated, the absence of data on unanesthetized ogs and the paucity of data on man. It will be convenient to consider e canine data first.

The hypothermic limit for anesthetized dogs subjected to cold-water nmersion is reasonably well established.[2, 3] It also may be said with asonable certainty that the mean lethal temperature (LT_{50}) is moderately fluenced by the specific preinduction anesthetic,[3] as well as by the degree respiratory assistance rendered during the course of cooling.[4] The former revealed in TABLE 1. Ether anesthesia, administered only until cold narcosis supervenes, permits evaluation of the LT_{50} independent of respirator assistance for, with the cessation of administration, further cooling progresse under conditions of spontaneous respiration. The latter, it is presume removed the major portion of the ether previously stored in the body, yield ing a preparation essentially free of any drug. The LT_{50} is approximatel 17° C. It is of some importance to note that this temperature is not altere when the respiration is assisted by positive-pressure artificial means whether air or oxygen is employed. That is to say, hypoxia appears not t be a contributory factor in the evaluation of the LT_{50} in etherized dogs.

Pentothal anesthesia, when initially induced and maintained by suppl mentary injections to bar return of consciousness, with or without complet

TABLE 2

MEAN TERMINAL HEART TEMPERATURES OF HYPOTHERMIC DOGS AT ONSET OF VENTRICULAR FIBRILLATION OR ASYSTOLE UNDER DIFFERENT ANESTHETICS

	Mean terminal heart temp. (°C.)		
	Pentobarbital	Ether	Pentothal
Fibrillary deaths..........	21.0	21.0	19.5
Asystolic deaths..........	17.9	15.8	16.1

blockade of the shivering reflex, depresses the respiration to an extent th becomes critical below 25° C. due to the added cold depression. The leth temperature thus would be determined in part by the adequacy of pulmonar ventilation or the onset of apnea. But if artificial respiration (again wi either air or oxygen) is supplied at 24° C. and lower, the LT_{50} is the same for etherized animals.

Pentobarbital, like Pentothal, requires that respiratory assistance rendered at temperatures below 25° C., and for the same reason. A stati tically higher LT_{50} obtains.

Thus are demonstrated the roles of artificial ventilation and of the speci preinduction anesthetic in the evaluation of the hypothermic LT_{50} in ane thetized dogs.

It remains to be determined whether such values bear any relation to th which obtains in the totally unanesthetized dog. It is quite possible th the LT_{50} would be higher in the latter; this is based upon an observati made on unanesthetized immersion-hypothermic human subjects at Dacha Because of the intensity of the shivering reflex, these men could scarce breathe. As they expressed it, it was as though their chests were encas in an iron band. It is, therefore, quite possible (although measuremen were not made) that pulmonary ventilation was inadequate and that hypox and hypercapnea were contributory to the high LT_{50} of 27° C. that obtain in the 7 subjects of the series. Hypercapnea and the consequent acido have been shown to raise the LT_{50} of anesthetized dogs by increasing the frequency of ventricular fibrillation (VF).[4]

The nature of death in the anesthetized hypothermic dog is also modified somewhat by the specific preimmersion anesthetic, as shown in TABLE 2. In general, a progressive bradycardia succeeds an initially accelerated heart rate. In some dogs the bradycardia progresses to asystole in the temperature range 18 to 14° C., whereas in most dogs VF interrupts the course of events at any temperature from 25° C. downward.[3, 6] As the table reveals, both the frequency and the mean temperature at which VF occurs are affected by the specific preinduction anesthetic.

TABLE 3

LETHAL HYPOTHERMIC TEMPERATURES (°C.) IN UNANESTHETIZED MAN SUBJECTED TO COLD-WATER IMMERSION*

Research number	Water temperature	Body temp. upon removal from water	Body temp. at death	Time in cold water (min.)	Time to death (min.)
5	5.2	27.7	27.7	66	66
13	6.0	29.2	29.2	80	87
14	4.0	27.8	27.5	98	106
16	4.0	28.7	25.0	60	74
23	4.5	27.0	25.7	57	65
25	4.5	27.0	26.6	51	65
?	4.2	26.7	25.9	53	53
Mean....	4.6° C.	27.7° C.	26.8° C.	65	74

An eighth subject survived 3 hours of immersion and a body temperature of 25.2° C.

* From the Alexander Report.[5]

The two most important and useful sources of information on lethal limits of hypothermia for unanesthetized man are: first, the literature search by Britton[7] of cases reported to 1930 (to which has been added the single case eported by Laufman[8] in 1951); and, second, the Alexander Report[5] of experiments conducted at Dachau during World War II. The former are cases of accidental exposure to subfreezing air temperatures, suffered predominantly by inebriates, whereas the latter deal with cold-water immersion.

In the Dachau experiments, 7 subjects were chilled to death, by intent, to determine the LT_{50} (TABLE 3). A value of 27° C. was obtained with a range from 24.2° to 29° C. and a mean exposure time of 65 min. to water of 4° C. an eighth subject survived a rectal temperature of 25.2° C. and an immersion of just under 3 hours). In another series of 57 experiments in which primary interest was directed elsewhere and in which chilling was routinely to a temperature below 30° C., there were an unstated number of deaths at unstated temperatures. Whether these deaths would elevate the value above the 27° C. found previously cannot be decided.

The estimate presented by Molnar[9] of survival time for men immersed in cold seas may be considered. From frustratingly incomplete data he arrived at a survival time of about 40 min. in water near the freezing temperature If this value be compared with the mean of 65 min. in the Dachau experiments, one must conclude either that Molnar's estimate is too low or that the LT_{50} for immersion of unanesthetized man is higher than 27° C.

TABLE 4 was arranged from the data given by Britton.[7] It suggests that the LT_{50} for unanesthetized man exposed to cold air is lower than that for cold-water immersion. Deaths were at the same mean temperature of 27° C.

TABLE 4
HUMAN HYPOTHERMIA RESULTING FROM EXPOSURE TO SUBFREEZING AIR TEMPERATURES (CASE REPORTS)

Inebriated		Insane oldsters survived
Died	Survived	
28.4	30	25.0
27.0	24	29.5
26.4	24.7	23.7
28.4	30.4	28.0
26.6	26.7	
	24.0	
	18.0	
Mean 27.4	25.4	26.5

but survival in the remainder was from a lower mean temperature, rangin down to 18° C. Involved here are certain variables that are not commo to the two means of hypothermia induction and that are worthy of consideration before drawing conclusions:

(1) The rate of cooling in water is considerably greater than in air. Th rate of heat loss may of itself affect the intensity of the shivering reaction and thus the ventilation.

(2) A degree of inebriation (common to the majority of the air-chille subjects) also could improve the respiration through partial block of th shivering reflex and thus indirectly affect the LT_{50}. A decision on the factors awaits the availability of directly pertinent data.

Regarding the nature of death in hypothermic man the data sheet presente is completely blank. To my knowledge there exists not one terminal electrocardiogram. From Dachau comes the merest hint. Holzloehner[5] describe the preterminal and terminal events with relation to heart action as follows (1) auricular fibrillation was invariable when the temperature reached 31 t 29° C., leading to arrhythmia perpetua; and (2) pulse regression led to preterminal rate of 40 to 50/min. (irregular) and its sudden disappearance he sudden disappearance of a reasonably strong beat suggested VF to olzloehner, but others disagreed.

In summary, the LT_{50} for the anesthetized dog subjected to immersion ypothermia is approximately 17° C.; for unanesthetized man it appears to e close to 27° C. A somewhat lower value obtains in man for cold air xposure. The nature of death in unanesthetized man appears to be VF hereas, in the anesthetized dog, it may be either VF at any temperature elow 25° C., or asystole in the range 18 to 14° C.

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LETHARGIC HYPOTHERMIA IN HIBERNATORS AND NONHIBERNATORS*

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When cooled, a homeothermic animal passes through several physiologica states.[1] After the first hypermetabolic state, the metabolic rate of the coole homeotherm gradually decreases and the lethargic state appears. Lethargi hypothermia has been studied in most cases in nonhibernators in which hypothermia has been induced for short periods of time. In this work lethargic hypothermia was induced (1) in a nonhibernator, the rat, which was maintained at a constant low body temperature for several hours; an (2) in a hibernator, the ground squirrel, also artificially cooled and maintaine in a lethargic state for several days. Oxygen consumptions during prolonge lethargic hypothermia, limits of lethargic states, and survival times of thes two different homeotherms when cooled have been compared. An attemp to prolong the survival in cooled, lethargic animals also was made. Th aims of those experiments were to demonstrate that animals cannot recove from severe hypothermia after a period, even though they are breathing, an to distinguish effects of hibernation from those of artificial cooling in th same species.

Procedure

Male 180 to 220-gm. white rats of the Holtzman strain and 150 to 250-gm ground squirrels of both sexes were used. Two different species of groun squirrels were used: *Citellus tridecemlineatus* and *Citellus citellus*. No di ferences in the survival, O_2 consumption, and other physiological processe were found between these two species.

Cooling was performed with Giaja's[2] technique, unless otherwise indicate The length of such hypercapnic-hypoxic cooling was about 1.5 hours for th rat (15° C. body temperature) and 2 hours for the ground squirrel (10° C body temperature).

Constant body temperature was maintained with the Adolph technique After cooling, the animal was placed in a 500 to 800-cc. glass cylinder an submerged in a constant temperature water bath. The cylinder was close with rubber corks at both ends and ventilated by an air stream previousl cooled in metallic tubing immersed in the water bath. The ventilation wa maintained at the constant desired level. The water bath was maintaine 0.5° and 1.0° C. lower than the desired body temperature for the rat an ground squirrel, respectively. The oscillations of the body temperatur were small (±0.2) throughout the experiments. Rectal temperature wa recorded with thermocouples. The difference in temperature between diffe ent organs in the body of the cooled rat was negligible.

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Rewarming was achieved in a 30° C. room. In some experiments the ewarming was initially speeded by placing the animal under a 100-w. bulb.

Oxygen consumption was measured in a closed-circuit apparatus[4] or with Pauling oxygen analyzer.[5]

Basal metabolic rate was determined in resting animals after 14 to 16 hours' tarvation at the temperature of their thermal neutrality (30 to 32° C.).

Summit metabolism[6] was measured at an external temperature of +2° C. fter the animals had been immersed in cold water up to the neck for 2 to sec.

Results

Chemical thermoregulation of homeothermic animals. The hibernator may e considered an imperfect homeotherm that hibernates when overcome by old. In order to assess the efficiency of temperature regulation relative to nonhibernator of the same size, the bioenergetics of active, winter ground quirrels has been compared with that of the white rat. In other words, the act that a hibernator hibernates during the cold winter months could be xplained in two ways. Either a hibernator is overcome by external cold hibernator falls passively into hibernation) or a hibernator is well protected gainst external cold and falls into hibernation actively. Gelineo[7] and ayser[8] found that in autumn and in winter the basal metabolic rate (BMR) f the indoor ground squirrel decreases unlike that found for the rat kept in a old room (Hart,[9] my data in TABLE 1). This fact was believed to be a sign f the appearance of an insufficient thermoregulation, but such insufficient hermoregulation was not confirmed. TABLE 1 indicates that, in spite of nuch decreased BMR, the winter ground squirrels have increased summit netabolism, increased cold response. Presumably the active winter ground quirrel does not differ from a rat, at least when the chemical thermoregulaion is taken for the base.

TABLE 1

OXYGEN CONSUMPTION OF WINTER AND SUMMER GROUND SQUIRRELS

Season	Number of animals	Basal metabolic rate		Summit metabolism	
		O$_2$ consumption in ml./kg./hour	Rectal temperature at end of experiment	O$_2$ consumption in ml./kg./hour	Rectal temperature at end of experiment
ummer......	14	1264 ± 86	36.8 ± 0.3	4955 ± 430	34.3 ± 1.3
Vinter.......	17	920 ± 68	36.7 ± 0.7	6630 ± 228	35.4 ± 0.7

Plus or minus standard deviation

The decrease in BMR probably is associated with the involution of endorine glands that takes place in ground squirrels during autumn and winter.[10]

The cold response and high level of summit metabolism in nonhibernators appear to require the normal functioning of the adrenals, particularly the cortex. After adrenalectomy the extra heat production of the rat drops almost to nil, and may be restored 90 per cent by injecting desoxycorticosterone (DOC).[11] Yet in the active winter ground squirrels the adrenal cortex is in the involution[10] and the extra heat production increases. The highly increased summit metabolism indicates a well-developed chemical thermoregulation, yet it is accompanied with a decreased BMR, opposite to what is seen in nonhibernators kept under laboratory conditions.

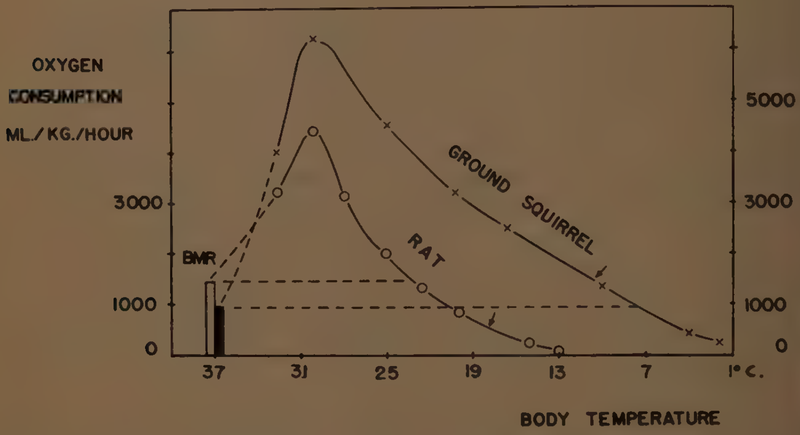

FIGURE 1. Oxygen consumption of winter animals (previously kept at 6° to 12° C. room) during cooling by immersion in cold water. Arrow indicates appearance of the lethargic state. The cooled rat becomes hypometabolic (related to BMR) below 23° C., the ground squirrel below 7° C. body temperature.

Ground squirrels kept in a 30° C. constant-temperature room will also hibernate.[12] To be able to enter into hibernation they must decrease their BMR. This also shows that the hibernators are not overcome with the external cold when entering hibernation. We have shown also that ground squirrels live without becoming hypothermic at external temperatures of −10° or −15° C.[12] Yet in nature (Yugoslav climatic conditions) the temperature of its burrows does not fall under +0.3° C. (data received from the Belgrade meteorological station show that the temperature of the soil at the depth of the burrows does not fall below freezing). These data indicate that the active ground squirrel does not differ from the rat so far as the chemical thermoregulation is concerned, and that the animal does not enter hibernation because it is overcome by external cold. If the difference between these two species is to be found in the cooled, lethargic state, it is not to be attributed to the difference in the active state, or to an insufficient homeothermia in the active winter hibernator.

Energetics of induced cooling. When heat loss overcomes heat production a homeotherm becomes hypothermic. Immersed in cold water, the rat and the ground squirrel follow similar metabolic patterns during cooling; the level of heat production increases at the beginning and then falls below the normal level as hypothermia progresses.

FIGURE 1 shows O_2 consumption during induced cooling in the rat and in the ground squirrel. In both animals the maximal O_2 consumption was found at the same body temperature, 30° C. The maximal heat production is a little higher than the previously recorded values of summit metabolisms (measured at higher body temperatures). Further lowering of the body temperature below 30° C. is accompanied by a greater lowering of the O_2 consumption in the rat than in the ground squirrel. At 23° C. body temperature in the rat, the O_2 consumption returned to the initial observed level, before cooling, in BMR conditions. The metabolic rate during hypothermia corresponding to the BMR occurs at 7° C. in the ground squirrel.

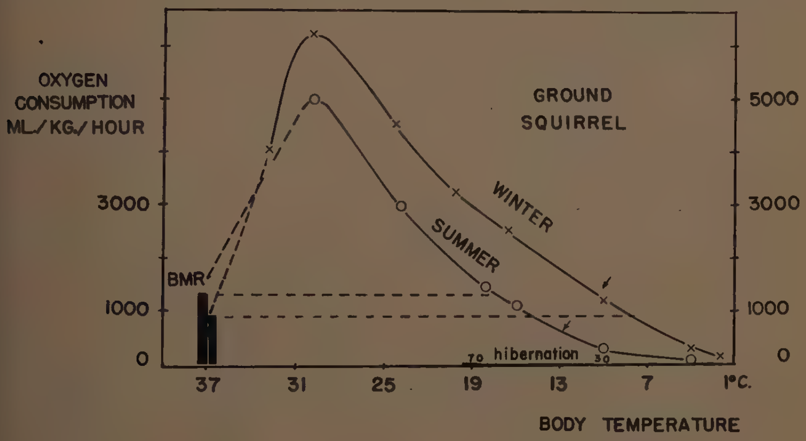

FIGURE 2. After determination of BMR, the ground squirrel was cooled by immersion in cold water and the O_2 consumption measured at indicated points. Arrow indicates appearance of the lethargic state.

Cooling below 23° C. in the rat induces further lowering of O_2 consumption, yet before the O_2 consumption is diminished considerably the lethargic state appears. In the ground squirrel the lethargic state appears even before the animal becomes hypometabolic (BMR taken as the base). The lethargic state appears in the same ground squirrel at higher or lower body temperatures and at different metabolic levels, depending upon the season when the cooling is induced (FIGURE 2). In winter animals, the upper limit of the lethargic state is found at a lower body temperature and at twice the metabolic rate found in summer animals.

During rewarming after short-term hypothermia, the level of O_2 consumption is the consequence not only of internal, but also of external temperature (FIGURE 3). The data I obtained show that both internal and external cold determine the level of O_2 consumption of the hypothermic rat. This happens within broad thermal limits of body temperature (20° to 37° C.).

In ground squirrels the same phenomena are observed. At 30° C. body temperature the O_2 consumption was 3920 ± 186 ml. O_2/kg./hour when the ground squirrels were rewarmed at 30° C. (room temperature), but it was 4807 ± 240 when they were rewarmed at 10° C. It also has been observed, in a ground squirrel waking from hibernation, that for the same body temperature of 30° C., O_2 consumption was higher in an animal waking at 5° C. than at 30° C. environmental temperature.[13]

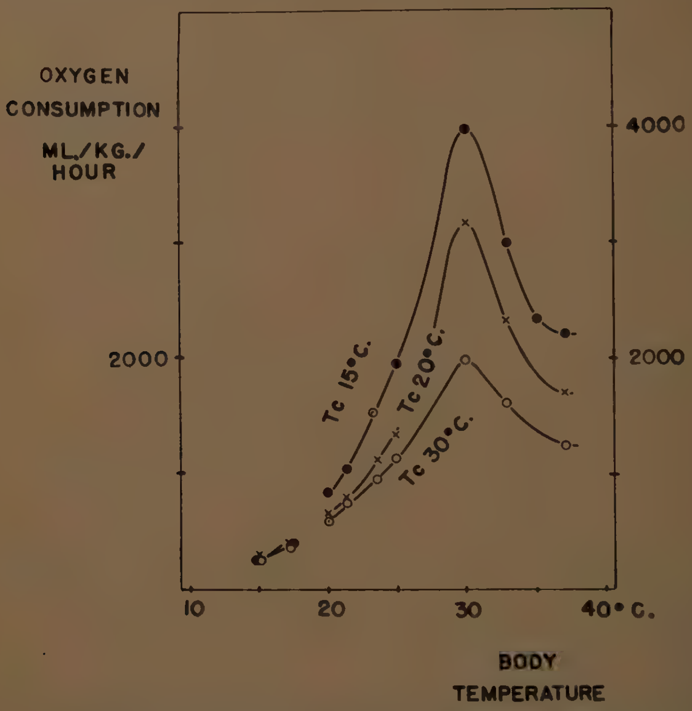

FIGURE 3. Rewarming of the rat after short-term lethargic hypothermia at different environmental temperatures. Tc = chamber temperature.

Below 20° C. body temperature, O_2 consumption of the cold rat is not affected by external temperature; the thermoregulatory mechanisms fail. Both lethargy and "artificial poikilothermia" appear at the same moment.[1-]

On the basis of my results I conclude that the active summer or winter ground squirrel, when cooled, follows the same metabolic pattern as a non-hibernator, the rat. Even a few hours before entering or reentering hibernation the winter ground squirrel develops a great cold response when artificially cooled. In no case did the animal follow the same pattern as when entering hibernation: decreasing the heat production parallel with lowering of body temperature.

Lethargic state. Limits of lethargic hypothermia are broader for the ground squirrel (between 10° and 2° C.) than for the rat (between 18° and 14° C.)

Above 10° C. for the ground squirrel and above 18° C. for the rat the animals are not lethargic. Below 2° and 14° C., respectively, breathing stops. However, it is possible to cool both animals lower and to revive them by using special techniques (Andjus[15] on the rat; Smith,[16] on the golden hamster). Oxygen consumption of the lethargic rat was at a fairly constant level during the first few hours if the body temperature was constant. At 15° C., the oxygen consumption was about 200 cc./kg./hour. However, the previous state, before cooling, also affected the lethargic state. Thus, for instance, it was found[17] that, while the O_2 consumption in 15° C. rats was 126 ± 17 cc./kg./hour if the animals were previously adapted to 30° C., it was 220 ± 27

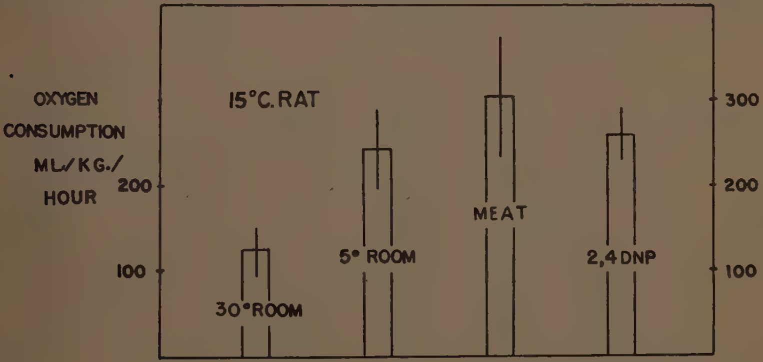

FIGURE 4. Oxygen consumptions of lethargic rats at 15° C. body temperature. Rats previously adapted to 5° C. environmental temperature or previously fed with meat or injected with DNP (from Giaja and Popovic[17, 19, 20]).

if the rats were adapted to lower environmental temperature (FIGURE 4). The O_2 consumption of the lethargic rat adapted to 5° C. environmental temperature was 75 per cent greater than that of rats adapted to 30° C.

The data I obtained in the 15° C. rat are in agreement with the results obtained on tissues *in vitro*. After adaptation of the animal to a colder environment, the O_2 consumption of isolated tissue slices was higher than in controls.[18] The O_2 consumption of the 15° C. rat was even higher when the animal was fed with meat before the cooling.[19] If 2,4-dinitrophenol was injected before or immediately after cooling, the oxygen consumption of the 15° C. rat also increased.[20]

The O_2 consumption in different species of rodents[21] varies widely when they are profoundly cooled[21] (FIGURE 5). "The law of the body weight" that Rubner found in homeothermic animals applies even when the homeotherms are deeply cooled, in the lethargic state. Similar regularities were found in poikilotherms,[22] but not in hibernators during hibernation.[23]

I conclude that during induced cooling the lethargic state appears in rats as well as in ground squirrels. The lethargy becomes more apparent in the rat with the higher body temperature than in the ground squirrel. The appearance of the lethargy is not to be associated only with the level of metabolism of the cooled animal. Winter ground squirrels become lethargic with O_2 consumptions 2 or 3 times greater than those of the rat or summer ground squirrel, respectively. The lethargic state appears in the winter ground squirrel even before the cooled animal becomes hypometabolic.

Survival times. The survival time of lethargic rats decreased about 2.5 hours for each degree of cooling below the body temperature of 18° C. The relationship between the body temperature and the survival time was linear

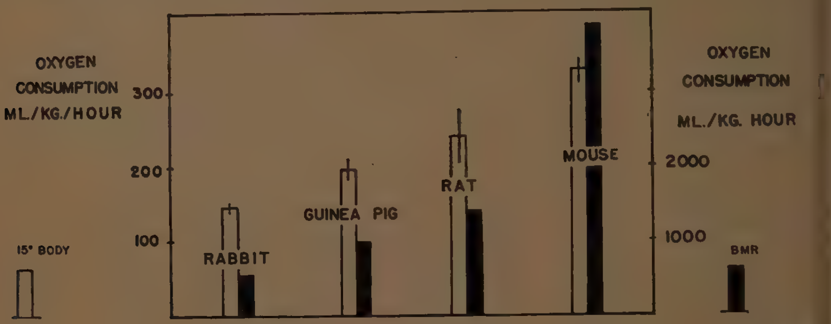

FIGURE 5. Oxygen consumption at 15° C. body temperature (*open bar*) and at 37° C. body temperature (BMR, *closed bar*). The O_2 consumption both before and after cooling is greater in the smaller animals.

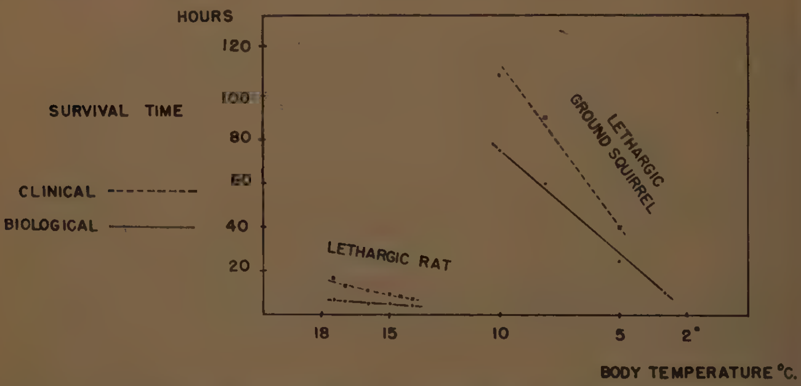

FIGURE 6. Survival times of artificially cooled lethargic ground squirrels and rats.

(FIGURE 6). At a 15° C. body temperature the survival of the lethargic rats was 9.5 hours, yet the rats could be revived only if the hypothermia did not persist more than 5.5 hours. Thus we may distinguish between biological survival (before the moment of biological death) and clinical survival.

In the cooled ground squirrel, the survival was also shorter when the body temperature was lowered. This is the opposite of what is found in hibernation, where the length of periods spent in hibernation increases with a decrease of the body temperature. For the same body temperature, both biological and clinical survival were longer in the ground squirrel than in the rat.

However, the absolute difference tended to decrease as the lower temperature limit of the lethargic hypothermia was approached.

Oxygen consumption. Once the body temperature of the cooled rat was stabilized at 15° C., the oxygen consumption was not changed during most biological survival (FIGURE 7). However, the O_2 consumption began to lessen a little before the moment of biological death and decreased continually until the clinical death. One hour before clinical death the O_2 consumption of the 15° C. rat was a third or less of the value the cooled animal exhibited before biological death.

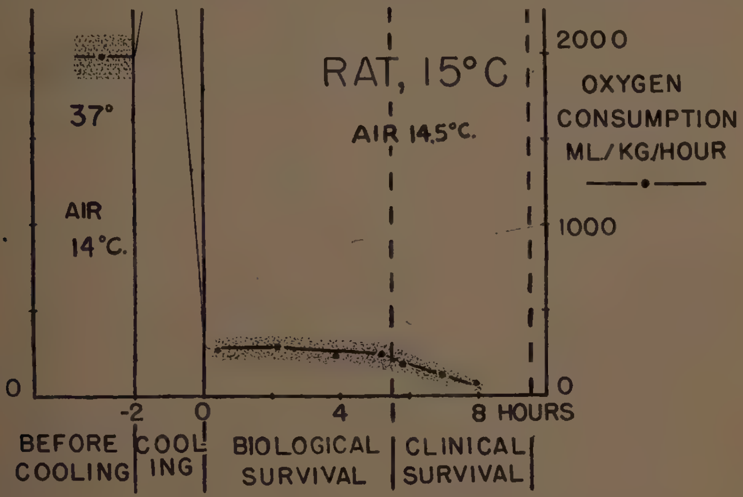

FIGURE 7. The oxygen consumption of the 15° C. rat.

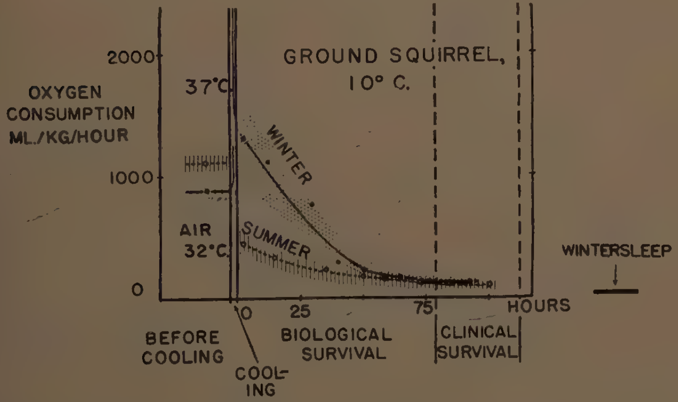

FIGURE 8. Oxygen consumption of artificially cooled ground squirrels with the same body temperature of 10° C. in winter and in summer.

In the 10° C. ground squirrel the initial high oxygen consumption (FIGURE 8) declined throughout the experiment, but even a few minutes before the clinical death it was 3 to 4 times higher than in hibernation at 10° C., and a little higher than in the 15° C. rat before its clinical death.

The O_2 consumption of the artificially cooled ground squirrel at 10° C. body temperature was dependent not only on time spent in lethargic hypothermia but also on season. During the winter, O_2 consumption of the artificially cooled 10° C. ground squirrel was 2.5 times greater than in the 10° C. animal during the summer. The difference between the O_2 consumption of winter and summer 10° C. ground squirrels tended to be smaller when hypothermia prevailed during a long time. After 50 hours or more of exposure at

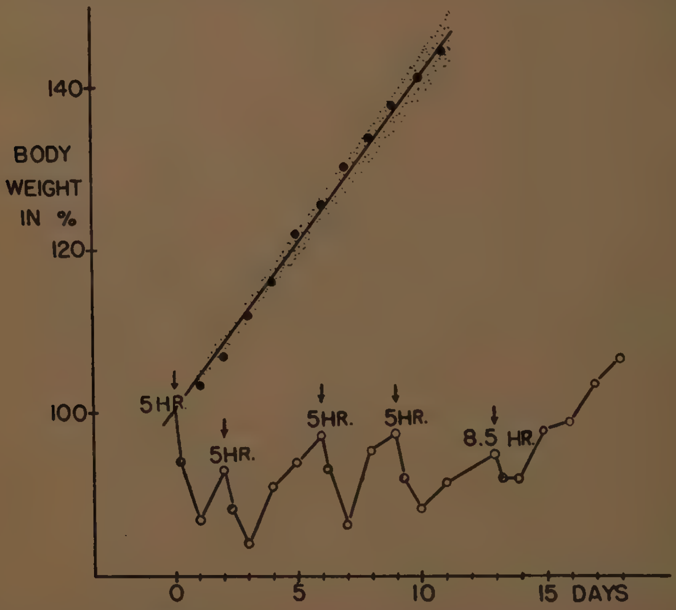

Figure 9. The body weight of rats cooled 5 times in 15 days to 15° C. and maintained at this body temperature for 5 hours. During the fifth cooling the hypothermia lasted 8.5 hours.

10° C. hypothermia the difference was nil. There was no difference in biological or clinical survival between artificially cooled summer or winter ground squirrels.

Postponement of biological death. The survival times, biological and clinical, depend on the body temperature. I have tried previously[24] to prolong the biological survival by using various treatments before or after cooling. Until now such assays have been unsuccessful. Injections of glucose and exsanguination with immediate transfusion of the blood of uncooled or cooled rats were without effect upon biological survival.

I report here two groups of experiments in which postponement of biological death was accomplished by "adaptation" to hypothermia or by interrupted exposure to hypothermia. In both cases the biological survival was augmented from 5.5 to 8.5 hours in 15° C. rats.

Adaptation to hypothermia was induced by cooling the rats for 5 hours, 4 to 5 times, once every third day. On the fourth or fifth occasion each rat was kept at 15° C. for 8.5 hours. Five of the 12 experimental rats biologically survived this prolonged cooling. During two weeks, as long as this experiment lasted, the rats (FIGURE 9) did not gain in body weight. During this time the body weight of the controls increased 50 per cent. Of the control rats, none survived 8.5 hours in 15° C. hypothermia.

Interrupted exposure to prolonged hypothermia also postponed biological death from 5.5 to 8.5 hours. Of eleven rats, 6 survived 8.5 hours in 15° C. hypothermia.

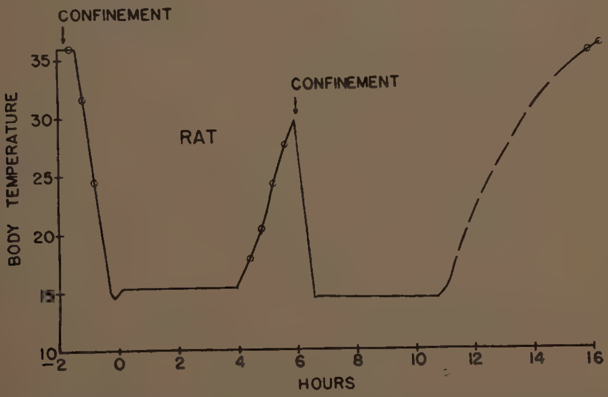

FIGURE 10. Interrupted exposure to 15° C. hypothermia postponed the biological death of the rat from 5.5 to 8.5 hours.

FIGURE 10 shows a typical experiment with interrupted exposure to hypothermia. The rat was cooled to 14.5° C. and held between 15 and 15.3° C. first for 4 hours, after which it was rewarmed to 30° C. in 2 hours. The rat was then recooled to 14.6° C. and kept for 4½ hours more at that body temperature.

I conclude that it is possible to prolong the biological survival of the cooled lethargic rat. Using the described techniques (adaptation to hypothermia or the interrupted exposure) the biological survival time was longer by more than 50 per cent.

Discussion

Two aspects of this work call for comment: (1) the inability of an artificially cooled lethargic homeotherm, nonhibernator or hibernator, to recover after a determined period from prolonged stabilized hypothermia; and (2) a striking difference between physiological states of the same animal, the ground squirrel, with the same low body temperature when artificially or naturally cooled (artificial cooling versus hibernation).

At 15° C. body temperature the rat lives about 9 hours, the artificially cooled 10° C. ground squirrel about 110 hours, yet both animals must be rewarmed before two thirds of the length of their survival has passed to be able to recover, that is, to survive biologically. In lethargic hypothermia biological death occurs first, the clinical later, contrary to what happens when the homeotherm is cooled to a greater degree. In "deep hypothermia,"[1] in suspended animation, clinical death occurs first, but rats can be reanimated from it.

The cause of biological death is not indicated by the data I have collected on the prolonged hypothermia of the rat and ground squirrel. Why a homeotherm is not able to survive a deeper lowering of its body temperature for a longer period of time is not known. It seems that temperature per se, above the freezing, does not damage any particular organ or tissue (during short coolings down to 0° C.). However, even a homeotherm-hibernator cannot survive lethargic hypothermia for an extended period, yet the same animal, with the same body temperature, lives for weeks in hibernation.

It is possible that long-term exposure to hypothermia damages some vital organ that could be considered as critical at the end of biological survival. It may be that enzymatic activity of the cells, functioning for a longer period at a new low level, becomes irreversibly damaged at the moment of biological death. The data obtained do not point to a particular vital organ as the critical one. The considerable change in O_2 consumption does occur after and not before the moment of biological death. A comparison between the hibernation and induced lethargic hypothermia indicates that the cause of death could be lack of coordination, or integrity, which became critical at the moment of biological death. In hibernation the vital mechanisms are present, but on a lower scale. Therefore the physiological functions are stabilized at a new level. This does not apply in prolonged hypothermia where the O_2 consumption, as do other physiological processes (reported elsewhere), are changing more or less with time.

From the fact that young rats, which have less developed thermoregulation, survive longer, one might have thought that the longer survival of the ground squirrels also was due to a poorly developed thermoregulation, as was often believed, but my finding on chemical thermoregulation in active ground squirrels eliminates this possibility.

Since Daubenton,[25] artificial cooling of hibernators has been performed in most cases to produce hibernation, but always with the same negative result. When cooling is artificially induced, the patterns of cooling are quite different from those observed in animals entering hibernation. The problem can be stated as follows: Is it possible to change from one pattern into the other one, to pass from the high-energy pattern to the low one (in hibernation) when one process had already started? It has been observed that, after a strong stimulus, the animal begins to wake and increases its O_2 consumption 10 to 15 times,[13] but if the stimulation does not continue the oxygen consumption sometimes returns to the previous level. All this happens without any significant increase in body temperature. If, as it appears, the rewarming from deep hypothermia, as well as the rewarming from hibernation, involves the same mechanisms (similar O_2 consumption at a determined body temperature), the answer is that the hibernator easily changes from low- to high-energy patterns and vice versa.

Conclusion

In this work the lethargic hypothermia has been induced in a nonhibernator, the rat and in a hibernator of the same size, the ground squirrel. Both animals were cooled by Giaja's technique or by immersion in cold water, and their patterns of cooling as the limits of the lethargic state were determined. By Adolph's technique the animals were maintained with constant-body temperatures, 15° C. and 10° C., for the rat and the ground squirrel, respectively, for hours or days, until death. The breathing and the heart stopped (clinical death) after 9.5 hours in the 15° C. rat and after 110 hours in the 10° C. ground squirrel, yet those animals biologically could survive only shorter period, not more than two thirds of the time they could survive clinically. Oxygen consumption, as well as the limits of lethargic hypothermia and the survival times, show that lethargic hypothermia in ground squirrels and rats is similar in nature, but quite different from natural hibernation.

Unlike animals in hibernation, nonhibernators and hibernators in prolonged lethargic hypothermia show considerable changes in O_2 consumption and probably in other physiological processes that lead to death.

Acknowledgment

Acknowledgment is made to E. F. Adolph for his help and advice throughout this work and to R. Busalkov for his assistance in its early stages. Thanks are also due to O. Heroux, J. S. Hart, F. Depocas, and Mrs. Dale Orchard for their help with the manuscript.

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FUNCTIONAL PROCESSES IN THE HEART AND THE POSSIBLE EFFECTS OF HYPOTHERMIA

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There are numerous techniques now available for studying various aspects of cardiac function. Many of them already have been employed to assay the effects of hypothermia on heart action and the functions of its parts.[1-3] However, a brief survey of the possible sites and modes of action of hypothermia may still be of some value as a prelude to consideration of new experimental results. It is very easy, for example, to think of many specific problems that newer microrecording techniques now permit us to study. I prefer to subdivide consideration of these numerous specific matters into two categories.

The first division of the subject is a study of the effects of cooling on specific structural elements and anatomical sites. The second division involves a consideration of the nature and relationships of: (1) membrane reactions and the electric response, (2) the activator process, and (3) the contractile response initiated by membrane depolarization and the attendant activator action. Multiple processes occur within each structural unit of the heart, and each of the functional processes mentioned involves chains of reactions. Indeed, the study of the changes brought about by cooling has many facets.

If we turn to the first category of thought, several problems may be perceived immediately. The heart is far from being a homogeneous structure. Not only are there differences in thickness of myocardial walls, proportions of connective and muscular tissue, blood supply, and innervation, but also marked differences in the cells that comprise the various parts of the heart. Cells of the sinoatrial node, the aortic wall, the atrioventricular node, the bundle of His, the Purkinje system, and the ventricular wall have been found to differ markedly in form and functional property.[3] Furthermore, there are junctional connections between these several cell types that have recently been found to exhibit special properties.[4-6]

New recording methods have permitted the study of junctional situations and better delimitation of the site of conduction failures.[6, 12] More will be said of this later, but it is obvious that the depressant action of cold is more likely to affect transmission in regions possessing low factors of safety. This use of hypothermia has not been exploited fully. It should be remembered also by those engaged in studies of the effects of hypothermia on the heart that even seemingly uniform inductions of hypothermia are likely to create temperature gradients because of dissimilarities of structure, blood supply, and metabolic characteristics of cells. Gradients must be sharp and relatively great to be of significance, however. This lack of homogeneity also should lead electrical engineers aiding cardiologists in studies of such factors as field effects, loops, moving dipoles, distribution of isopotential lines, and cancellation coefficients to consider temperature change a matter of great import.

Anatomical difference indicates functional difference, and the nature of structure ultimately must be considered in any functional analysis. A structural element of known major importance in the heart is the cell membrane. Our best methods for studying activity within this structure are the electric recording techniques; this introduces the second division of general consideration that has been suggested: the study of cardiac action.

During the basic resting state, metabolic activity is necessary to maintain membrane polarization and a partition of ions that appears to be essential to normal cellular function. The activity of ion exchange pumps is not very sensitive to cold. Temperatures must be reduced to 24 to 28° C. before significant changes occur in resting potentials.[2, 8] Extreme cooling, however, does affect excitability and modifies the threshold potential.[3, 9] In hypothermia the membrane is either more stable, or the regenerative processes of depolarization are more difficult to trigger. There is evidence that in the heart, as in the nervous system although reactions are more difficult to evoke, there is, at early stages of cooling, a degree of overaction. Action potentials are much more prolonged, although little reduced in amplitude, and constitute more effective intrinsic stimuli. There is reduction of adaptability (accommodation), and the possibility of repetitive response from single stimuli becomes apparent. Furthermore there is some evidence that on rewarming, there is a lag in recovery of some characteristics over recovery in others. Aftereffects of hypothermia have been observed, and they suggest consideration of acclimatization and its reversal.

It has been known for many years that cooling reduces heart rate, but only recently has it become possible to study the basic processes of pacemaker action. Cooling causes a profound slowing of the spontaneous depolarization occurring in pacemaker cells, and the Q_{10} of the rising phase of the prepoten~~tial has~~ been determined.[9, 10]

The action potentials of most body cells show a quick rising phase, an overshoot, a repolarization or descending phase, and afterpotentials. Some heart cells, the Purkinje and ventricular fibers of most species in particular, reveal a peculiar plateau phase subsequent to the overshoot and preceding a swift terminal repolarization phase. These cells also fail to show any clearly definable afterpotentials of an orthodox nature.[3, 11] The Q_{10} of each of these phases is characteristic and the variation seen supports the obvious assumption that the chemicophysical processes involved are peculiarly susceptible to the effects of cold.[2, 3] The plateau phase of the action potential differs most significantly in hypothermia. A combination of the use of hypothermia and chemical methods is certainly indicated in studies of the electric response of the heart and its individual cells.

Repolarization does not of itself restore normal excitability, and evidence has been obtained suggesting that hypothermia may increase this discrepancy.[3] It is difficult to study associated and interdependent processes. The relationship between membrane depolarization and the initiation of contraction has not been amenable to study. Repolarization is completed before recovery of the contractile process; therefore, it is possible to initiate in the mammalian heart an extra electric response that is unaccompanied by a contraction of detectable magnitude. There is, however, a long-persisting effect that ultimately does modify the contractile process.[1, 3] It is quite possible that hypothermia might still be of use in exploring the mysteries of this interaction.

Physiological chemists have been much concerned during late years with the chemistry of muscular contraction. Cold has been used as an adjunct to many *in vivo* and *in vitro* experiments of this category.[13, 14] Certainly, cooling modifies the contractile force of the heartbeat and the cardiac output.[15]

The very practical matter of ascertaining the usefulness of hypothermia and of determining factors responsible for production of asystole and/or fibrillation during hypothermia involves consideration of the basic processes mentioned above. If one considers the possible causes of fibrillation, the development of ectopic pacemakers under conditions that exceed the resolving power of the heart (ability to maintain integrated action) and abnormalities of conduction due to changes in the strength of the propagated excitatory process associated with an abnormal dissimilarity of ability of cardiac elements or regions to respond, one readily perceives that, in hypothermia, more than one contribution to vulnerability could develop. The problem is to isolate and identify the major contributory changes.

In pursuance of this line of thought, namely that multiple processes occur that are differently affected by cooling, it is not surprising to encounter the claim that the usefulness of certain antifibrillatory drugs is lessened in hypothermia and that other agents become useful. It is certainly possible that the cause of disorganization of cardiac action in hypothermia is distinctly different from the causes of fibrillation in the normothermic heart. Fibrillation is due to disorganization of the activity within the heart, and such states are certainly produced by different causes and integrative failures.

Hypothermia may be employed with any one of a number of purposes in mind. It can be employed as a tool in the analysis and identification of functional processes; it can be used to reduce organ activity and the demand imposed on the heart with respect to maintenance of blood flow; conceivably, it could be used to protect the heart itself from the consequences of a coronary deficiency.[7] It is used to slow down ion fluxes and reactions to ionic changes so that they can be studied better. Hypothermia is being used in those studies that appear to me to be next in order of importance: the consideration of enzyme and metabolic processes involving cellular cytoplasm and membranes that maintain the membrane, serve as carriers, restore normal resting states after activity, and participate in the touch-off and the actions involved in the responses initiated by intrinsic and extrinsic stimuli.

All processes within the heart are subject to some control. The neurohumoral mediators produce the required moment-to-moment modulations, but endocrine glands and the presence of agents originating from other sources can affect cardiac states to a marked degree. Hypothermia can affect cardiac control mechanisms directly and indirectly.

It is felt that, as we proceed to a consideration of specific investigations f the heart and hypothermia, we should keep in mind the basic problems nd some such classifications of our ideas as those proposed.

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EXCITABLE PROPERTIES OF THE HYPOTHERMIC HEART*

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There are both academic and practical reasons for study of the hypothermic heart. Our own interests, centered as they are upon the extreme susceptibility to ventricular fibrillation (VF), could be classified either way. Experimental effort has been directed variously toward (1) discovering conditions that might influence the frequency of fibrillary deaths, (2) investigation of those functional properties most readily susceptible of measurement, alterations which might yield clues as to causation, and (3) pharmacological control. This paper is concerned primarily with changes in readily measurable functional properties in the dog heart *in situ*.

Hypothermic VF occurs quite spontaneously, the stimulus being apparently intrinsic. It rarely occurs, however, at temperatures above 25° C., either during induction or rewarming.[1] In general, it is preceded by some ectopic action, and it is presumed that an ectopic beat serves as the trigger. Fibrillation can be readily induced also by a variety of extrinsic electric, mechanical, and other stimuli. For this there appears to be no highly critical temperature, as even at 30° C. (the temperature which most cardiac surgeons have assumed to be optimum) ventriculotomy and ventriculography all too frequently precipitate VF.[2] This is not to suggest a qualitative difference between the spontaneous and induced varieties, but rather that the threshold for fibrillation (FT) is graded with respect to heart temperature. Thus, at 25° C. and lower the threshold is attainable by *spontaneous* ectopic action, whereas at higher temperatures a stronger stimulus is required, as experimental testing bears out.

Dogs that escape VF during hypothermia induction cool to lower temperatures with progressive bradycardia and ultimate asystole in the temperature range 18° to 14° C. At this point the heart usually will be found unresponsive to electric stimuli,[3] the explanation for which is apparently to be found in measurements of transmembrane potentials.[4, 5] At low temperatures membrane repolarization fails and therefore excitation becomes impossible.

As a first approximation it might be supposed that myocardial fibers are rendered hyperexcitable by cooling, a state that, when coupled with development of ectopic foci, would lead readily to VF. This is obviously an oversimplification unless it be assumed that VF develops only in localized areas that to date have eluded detection.

One may suppose with greater justification that temperature change affects differentially such properties as refractoriness, conduction velocities, and other functions of the several specialized cell types, and that when imbalance among these functions reaches a critical value the stage is set for triggering.

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A reasonable beginning, if only for purposes of elimination, nevertheless appeared to be the measurement of the excitable characteristics of the cooled heart via construction of strength-interval and strength-duration curves for comparison with normal hearts. From these would be revealed alterations in thresholds and refractoriness as a function of cardiac temperature,[6, 7] which might be useful in relation to existing hypotheses to account for fibrillation in general.[8]

Strength-Interval Curve

This is obtained by plotting excitation thresholds throughout the cycle against the time within the cycle. In FIGURE 1 are plotted curves obtained in one dog at normal temperature and two hypothermic temperatures. The latter differ little from the former except in time relations, that is, the dura-

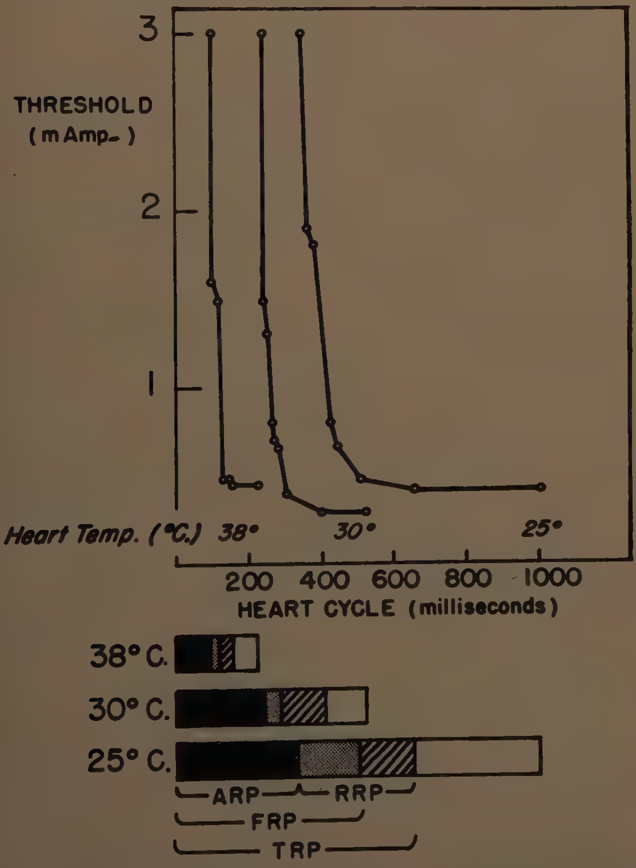

FIGURE 1. Excitability cycle of the dog ventricle at normal and low temperatures.

tion of refractoriness. The irregularities in the descending portion of the curve, which marks the end of absolute refractoriness (the "dips" of Orias *et al.*[9]), are essentially unaffected. It may be noted in passing that these irregularities are more characteristic of the anesthetized than of the unanesthetized animal,[10] but it has not been determined whether they are peculiar to pentobarbital anesthesia.

The most characteristic effect of cold on these curves (other than lengthened refractoriness), which is not revealed in plots on the scale of FIGURE 1, is the indistinct termination of the total refractory period (TRP). Instead of the usual smooth transition to diastolic threshold, the latter is reached by way of a series of very shallow steps. If one describes the dimensions of the steps in terms of "tread" and "rise," the former are of the order of 50 to 100 msec., while the latter are measured in hundredths of mAmp. This phenomenon makes difficult the determination of the outer limit of the TRP as compared to the absolute refractory period (ARP), which is measured with equal facility at normal and low temperatures.

TABLE 1
VENTRICULAR EXCITABILITY AND REFRACTORINESS DURING PROGRESSIVE HYPOTHERMIA*

	Heart temperature (C.)			
	38°	30°	25°	20°
	(6)	(6)	(5)	(2)
Auricular driving diastolic threshold (mAmp.)	0.5	0.5	0.5	0.6
	(30)	(26)	(17)	(3)
Ventricular driving diastolic threshold (mAmp.)	0.4	0.4	0.5	0.8
Heart cycle (msec.)	345	510	925	1800
ARP (msec.)	140	220	365	550
TRP (msec.)	165	295	490	920
FRP (msec.)	170	295	460	730
TRP-ARP (msec.)	25	75	125	370
FRP-ARP (msec.)	30	75	95	180

* These values are rounded to the nearest 5 msec. or 0.1 mAmp.

Diastolic thresholds, as measured with bipolar electrodes, are only slightly affected by temperature down to 25° C., but tend to rise at lower temperatures, as shown in TABLE 1. Since driving and testing stimuli were delivered via the same ventricular electrodes, the possibility that driving stimuli might affect excitability to testing stimuli was checked in a series of 6 dogs in which driving stimuli were delivered to bipolar electrodes attached to the right auricle, and further checked in these animals by alternate auricular and ventricular driving. It was found that ventricular thresholds were essentially the same regardless of mode of driving, as shown in TABLE 1.

Also recorded are refractory periods at the several temperatures, together with the corresponding heart cycles. Both ARP and relative refractory period (RRP) contribute to the marked lengthening of the TRP. This is probably to be anticipated if all phases of repolarization are based on enzymatic processes.[4] Nevertheless, the effect of hypothermia on the RRP may be contrasted with its relative constancy at normal temperature regardless of rate (or cycle duration) within the normal physiological rate range. Also of interest is the observation that, whereas the functional refractory period (FRP) and TRP are almost identical at normal temperature, a considerable disparity develops with cold. Defining FRP as the interval between the response to a driving pulse and the earliest obtainable conducted response (with the same latency) to a test pulse, it would appear that responsiveness recovers sooner than excitability (measured by return of diastolic threshold). Similarly, if the end of FRP coincides with completion of repolarization as measured by transmembrane potentials, repolarization in hypothermia is complete prior to recovery of diastolic excitability.[6, 11] However, this requires verification.

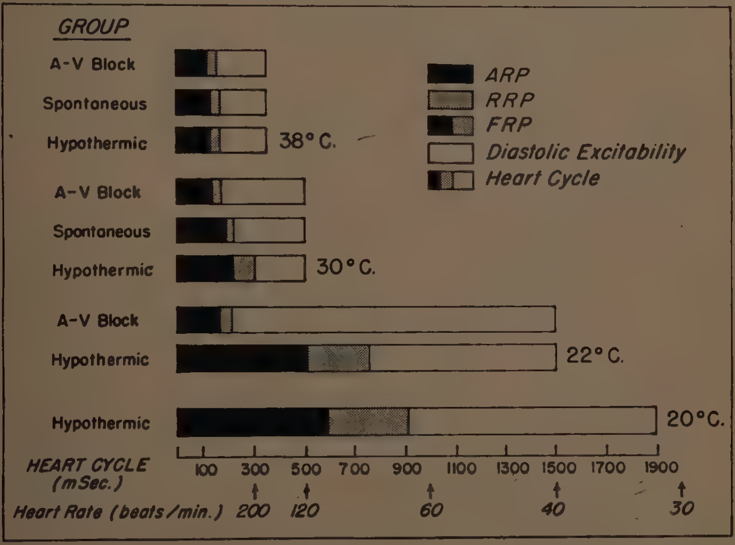

FIGURE 2. Ventricular refractory period and heart rate in normothermic and hypothermic dogs.

That the lengthened refractory period and the several segments thereof are consequent upon temperature rather than the concomitant bradycardia is established by examination of the cycles in corresponding degrees of bradycardia at normal temperature. This is possible in the preparation in which complete heart block is surgically produced. By driving the ventricle in such a preparation at the rates that prevail at the several hypothermic temperatures, it is found that both ARP and TRP are but slightly dependent upon cycle length (FIGURE 2).

Strength-Duration Curves

Even though the mean diastolic thresholds measured with bipolar stimul of 1-msec. duration appear relatively constant to 25° C. (TABLE 1), strength-duration measurements reveal a progressive rise in threshold with temperature depression.[7] This obtains for both anodal and cathodal stimuli. The shorter the stimulus pulse, the greater is the temperature effect. It is not self-evident in the conventional plot of strength-duration curves (FIGURE 3)

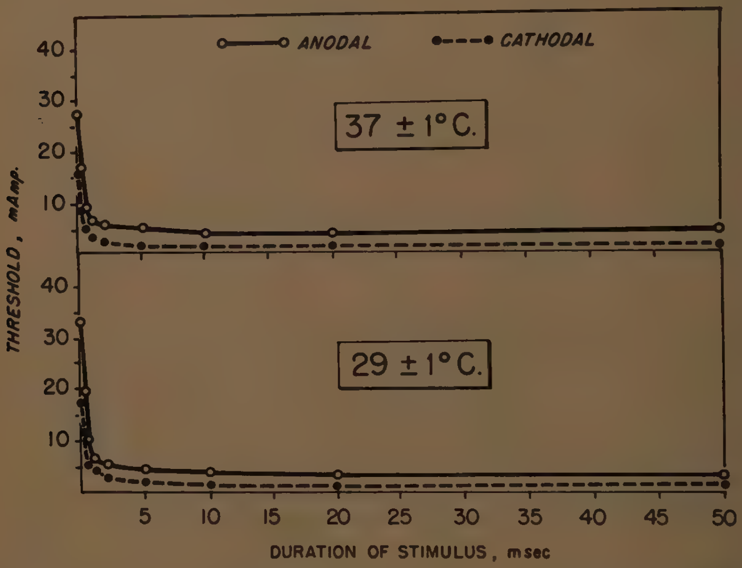

FIGURE 3. Cathodal and anodal strength-duration curves at two stabilized temperatures

but by plotting stimulus intensity against the reciprocal of stimulus duration rectilinear graphs are obtained that reveal the temperature effect in the respective slopes. The graphs thus obtained (FIGURES 4 and 5) fit the expression

$$i = m\,1/t + r \qquad (1)$$

where i = threshold intensity, m = slope, t = stimulus duration, an r = intercept = rheobase, since $i = r$ when $t = \infty$.

A comparison of the slopes at 38° C. and at 29° C. (FIGURE 4) reveals tha the rise in threshold is considerable for short pulses and almost negligibl for rheobasic pulses and that anodal stimuli are more affected than cathodal as indicated by the slopes. Chronaxie, which is indicated by stars in th figure, is minimally affected; furthermore, it is possible to show that chronaxi is simply a function of slope and rheobase. Thus, t_c is chronaxie when threshold current $i = 2r$; by substituting this value of i in EQUATION 1 it can b shown that $t_c = m/r$.

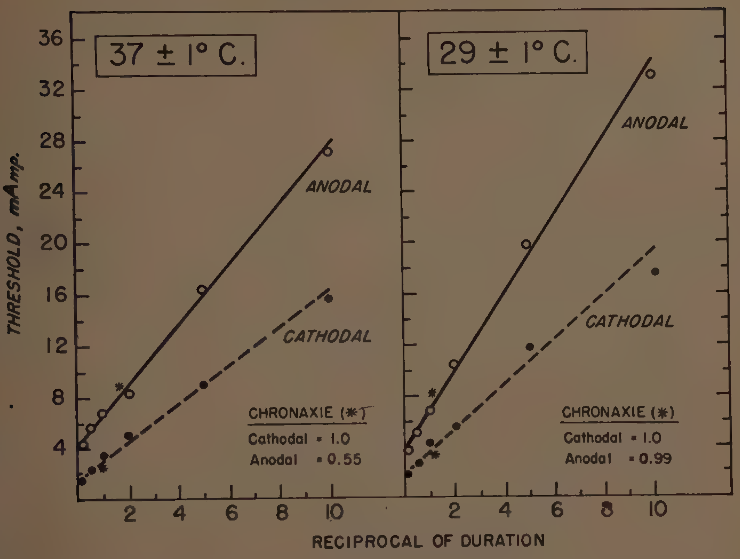

Figure 4. Straight-line transformation of unipolar strength-duration curves, demonstrating increased slope with cooling.

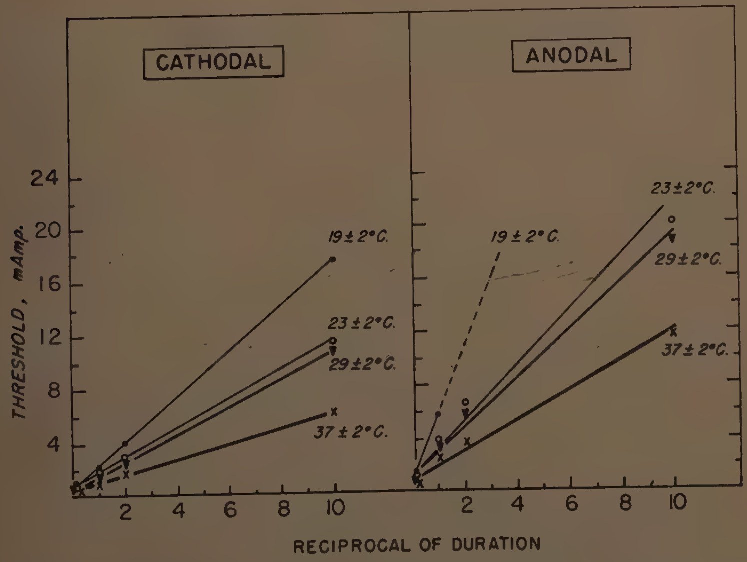

Figure 5. Comparison of unipolar strength-duration lines obtained during continuous cooling at four temperatures.

In FIGURE 5 is demonstrated the progressive nature of the changes wrough by temperature, as noted in 5 dogs. Each point on each curve is thus the average of 5 measurements.

These observations on cold-induced threshold changes are not unique but have long since been reported for nerve[12, 13] and, more recently, fo skeletal muscle.[14] The explanation for the apparent differential effect on short versus long pulses is also to be found in previous observations, which indicate a loss of accommodation at low temperatures.[15] The effectiveness of the property of accommodation in relation to very short pulses is negligible at any temperature, so that the effect of cold is revealed predominantly in a rise in threshold. The same effect on thresholds in relation to long pulses apparently is masked by the simultaneously diminished ability of the tissue to accommodate.

Whether the loss of accommodation can be written into a reasonable hypothesis for the genesis of hypothermic VF is a question. It has been so employed by Hoff and Stansfield[16] and by Scherf *et al.*[17]

Fibrillation Thresholds

The rather modest depressant effect of hypothermia on the excitability o the heart stands in marked contrast to the concomitant effect on irritability, so evident in the ease with which fibrillation is precipitated. Since no single method can be relied upon as a measure of this susceptibility, several approaches have been employed. The results presented here are preliminary and require both amplification and refinement for a reasonable interpretation

TABLE 2
MEAN VENTRICULAR FIBRILLATION THRESHOLDS TO LONG (3 SEC.) DC SHOCKS

	Bipolar (4) (mAmp.)	Anodal (9) (mAmp.)	Cathodal (9) (mAmp.)
Normothermia (38° C.)..........	6.4	6.2	9.4
Hypothermia (25° C.)...........	3.8*	5.3	6.9*

* Significantly different from normothermia ($p < 0.05$).

In general, fibrillation thresholds (FT) were measured for known anodal and cathodal currents of long and short duration. The former were employed for two principal reasons: (1) they are effective in initiating VF in normothermia at relatively low intensities (2 to 10 mAmp.), whereas short pulses require more than 30 mAmp. and, (2) it was felt that the longer shocks, extending over several cycles, would stimulate certain conditions that might exist *in vivo*, such as currents resulting from differences in oxygenation, temperature gradients or, possibly, true injury currents. By contrast, shocks of 1 to 10 msec., when delivered during the recovery phase of the cardiac cycle, may be more akin to currents resulting from differences in rate of recovery of different parts of the myocardium.

The thresholds obtained for long DC shocks, both bipolar and unipolar, are given in TABLE 2. For bipolar and cathodal shocks the fibrillation hreshold is significantly less at 26° C. than at normal temperature. Conrary to expectation, however, the threshold to anodal current remained relatively constant. Therefore it would appear that anodal currents are not basic to the susceptibility to VF.

Excitation is dependent to a considerable extent upon rate of change of applied current, as well as upon intensity. It was therefore desirable to discover any changes in FT to several frequencies of sine-wave currents applied

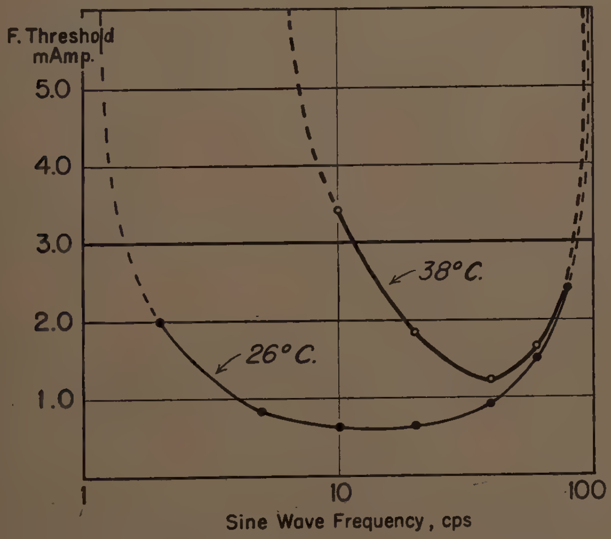

FIGURE 6. Fibrillation thresholds to sine-wave currents of 3-sec. duration at 2 stabilized temperatures.

for 3 sec. The mean values obtained on 7 dogs are given in FIGURE 6. The changes due to hypothermia were encountered in every dog. It is noteworthy that with the most effective frequencies the intensity required to produce fibrillation is very small.

To determine the dimensions of the vulnerable period and its threshold at low temperatures, unipolar stimuli of 10-msec. duration were delivered at known points in the cycle. Excitability and refractory periods were measured concurrently while the control of the rate was maintained by driving. From a total of 42 determinations in 4 dogs, employing both anodal and cathodal shocks, excitability and RP data were obtained similar in all respects to those discussed previously. Additionally, it was noted (FIGURE 7) that: (1) the period during which anodal excitability exceeds cathodal[9, 18] increased from the normal of approximately 10 msec. to 30 msec. at 26° C.; (2) FTs drop from a value greater than 30 mAmp. at normal temperature to 2 to 4 mAmp. in hypothermia; (3) the period in the cycle during which the

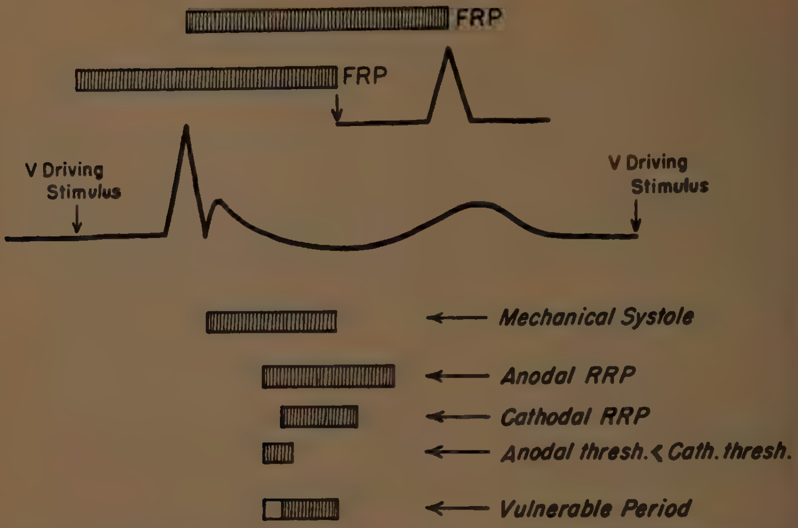

FIGURE 7. Relation of several cardiac events to the cardiac cycle, measured from ventricular driving stimulus as zero time.

FT could be reached with low-intensity currents at the low temperature was 80 to 100 msec., and within the limits of the RRP; (4) the vulnerable period is less than the RRP as measured with either anodal or cathodal pulses, and is not clearly related to the period during which anodal excitability exceeds cathodal (more refined measurements are required to define this relationship); (5) the vulnerable period appears to be coextensive with the final one third to one half of the contraction phase of the cycle; and (6) beyond the limits of this period, FTs could not be reached with pulses as intense as 30 mAmp.

The fact that a vulnerable period with a very low threshold exists for 80 to 100 msec. during the RRP at 26° C. (TABLE 3) yields a partial explanation for the ease with which fibrillation may be precipitated, either spontaneously or

TABLE 3
RELATIVE REFRACTORY PERIOD IN HYPOTHERMIA

Temperature (centigrade)	Percentages of TRP			Percentages of cycle		
	38°	25°	20°	38°	25°	20°
RRP	15	25	40	7	13	21
ARP	85	75	60	41	40	30
TRP	100	100	100	48	53	51

Vulnerable period at 25° C. = 75 per cent of RRP.
Threshold = 2 to 4 mAmp.

by extrinsic stimuli. This represents a considerable period during which the production of a 2 to 4 mAmp. current (by whatever means) could throw the ventricle into disorganization. How is this low threshold for fibrillation brought about? It would be helpful if clues could be found in single-fiber preparations studied by the newer techniques. A decision might be reached on the question whether the low FT is a property of a fiber population or whether it is explainable on the basis of individual cell properties. At present, there is ample room for speculation, but a logical approach must await the availability of more information.

Still another type of FT was investigated: that related to excessive heart rates. The ventricle was driven by means of 1-msec. rectangular bipolar pulses until fibrillation occurred. This type of experiment is complicated by the severe hypotension associated with fast driving rates, so that one cannot be certain that rate, rather than coronary flow, is critical for the onset of fibrillation. In any event, on the basis of 3 to 4 measurements in each of 3 dogs the critical rate at normal temperature was 490 bpm, whereas 260 caused fibrillation at 26° C. Again, the change caused by hypothermia proved to be consistent.

One cannot escape the conclusion that the fibrillation threshold, however measured or defined, is remarkably low. The fibrillation threshold can be defined only in terms of the experimental stimulus employed to provoke fibrillation and, when so defined, there is no commitment regarding the nature of the pathophysiological stimulus, its mode or site of action, or the nature of the functional change in cells or syncytium that make the stimulus suddenly effective. One may nonetheless reasonably assume that the degree of temperature drop grades the responsiveness to the pathophysiological trigger as it does to the multiplicity of experimental triggers. It would be less reasonable to suppose that the heart tissue remained functionally normal and that the hypothermic state produced only a peculiar and undetermined kind of trigger that could send an otherwise normal heart into fibrillation. Only a functionally deranged heart could be triggered by stimuli so diverse, stimuli that at normal temperature are relatively impotent.

If any one of these quantitative measures of the FT was also quantitatively related to the susceptibility of VF in individual animals, it should be possible to predict in the individual case which dog would survive ventriculotomy and which would most likely succumb to VF. However, to date this has not proved possible. There seems to remain an unknown and unquantitated factor, apart from these electric FTs, that determines the susceptibility to fibrillation, whether spontaneous or induced. This is apparent from the data presented here and those of Covino and Beavers,[19] who report that neither *p*H control nor prior cold acclimatization in dogs influences the FT to electric pulses delivered during the vulnerable period, yet both of these factors modify the incidence of spontaneous VF.

Controlled Heart Rates

Recently Riberi *et al.*[20, 21] have reported that selective blockade of the S-A node with a local anesthetic provided protection against hypothermic VF, including that so frequently induced by ventriculotomy. Protection by thi means would appear to be due either to some factor related to the rate an rhythm of the S-A nodal discharge or a modification of A-V conduction If one of these provided the explanation for protection, then equally successful should be control of heart rhythm by auricular driving or elimination o A-V conduction via ventricular driving.[22] However, 5 dogs in which rate and rhythm were controlled by auricular driving all succumbed to VF at a mean temperature of 21.3° C. and from mean rates of 67 bpm. Driving

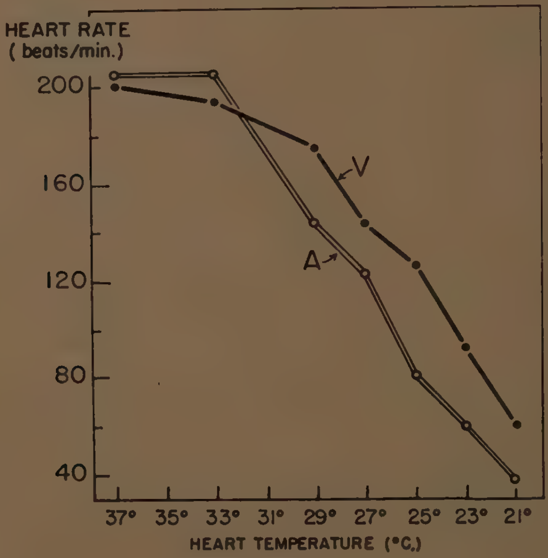

FIGURE 8. Auricular and ventricular driving rates during progressive hypothermia t terminus in dogs.

was maintained throughout at a rate just greater than the spontaneous at all temperatures (FIGURE 8), and with due regard to the adequacy of the blood pressure. Isolated ectopic action was neither recorded nor observed in any animal prior to the onset of fibrillation.

In another series of dogs subjected to ventricular driving to eliminate possible A-V conduction abnormalities, the end result was the same. VF occurred in all at a mean temperature of 20.3° C. and mean heart rate of 67 bpm. Ectopic action was conspicuous in 3 of the 5 dogs prior to fibrillation. This is not due necessarily to escape of auricular impulses across the A-V node and bundle, since such ventricular extrasystolic action occurs also in hypothermia induced after surgically produced heart block.

The nature of the protection afforded by S-A nodal block remains an unresolved problem, as is the causation for susceptibility to VF in the hypothermic state. The data here presented, when considered in isolation, yield no real clues to the latter problem. Revealed only is the prolonged period of relative refractoriness during most of which the ventricle is extremely vulerable to weak stimuli (2 to 4 mAmp.), and the diminished ability of the issue to accommodate. Thus, while excitability is decreased, vulnerability greatly increased. In Brian Hoffman's discussion elsewhere in this monoraph, the suggestion is made that the loss of the ability to accommodate, oupled with the slow rate of repolarization, may induce spontaneous firing ach time the repolarization reaches the critical level at which regenerative epolarization would normally occur. If this be so, then a rather modest mount of asynchronie in the repolarization process throughout the ventricle ould account for fibrillation even in the absence of a triggering ectopic beat r application of an extrinsic stimulus.

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HYPOTHERMIA AND VULNERABILITY

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I am never surprised to see a mammalian heart fibrillate under condition of hypothermia. To the contrary, I am much more surprised that the normothermic heart is not more prone to fibrillation than seems to be the case. I we consider the possibilities for disorganization in the mammalian hear presented by multiple fibers capable of pacemaker activity, multiple fibe types with action potentials of different durations and differing excitability and with multiple pathways for each impulse to traverse, it is apparent tha regular organized activity is maintained only by an almost perfect adjustment and coordination of all aspects of excitability and conduction. A C. Mc. Brooks states elsewhere in this monograph, a change in temperature i known to affect many of the reactions associated with electric activity o cardiac fibers to a different degree; hence, disorganization is a likely sequel o hypothermia.

In a consideration of the increased vulnerability caused by lowering th heart temperature to 25° to 20° C., however, it is possible to mention severa distinct causes of fibrillation and to evaluate each in the light of the result of recent studies. The hypothermic heart may fibrillate because of stimulation from an extrinsic source, such as that due to surgical intervention, o from the activity of one or more ectopic pacemakers. Fibrillation migh also occur in the absence of any pacemaker activity because of persisten depolarization in some area or simply because of disorganization of the sprea of activity. We can disregard fibrillation induced by surgical manipulation for the moment and consider the likelihood of the other three mechanisms

Studies of pacemaker activity in single Purkinje fibers[1, 2] and in fibers o the sinoatrial node[3] have shown that in isolated preparations of cardia muscle a progressive lowering of temperature decreases diastolic depolarization and ultimately leads to loss of intrinsic rhythmicity. Enhanced pacemaker activity thus is rarely encountered when isolated preparations ar cooled to temperatures of 10° to 15° C. unless the change in temperature i quite rapid.[4] In the intact heart, however, records of Purkinje fiber activity during hypothermia have not yet been obtained. The possibility remains nevertheless, that in some critical temperature range the fibers of the specialized conduction system develop increased pacemaker activity. Anothe possibility is that, in the absence of sufficiently rapid excitation from th sinoatrial node, several ventricular pacemakers escape from sinus domination and thus initiate ectopic ventricular activity. The results reported by A. H Hegnauer elsewhere in this monograph make this mechanism unlikely, since hearts driven from either atrial or ventricular electrodes at rates somewha in excess of the spontaneous rate for each temperature fibrillated at the same temperature as undriven hearts. Under these conditions the sudden an undetected activity of a ventricular pacemaker might again be the causa agent. However, if this is the initiating factor for fibrillation, it seems as though some other mechanism must also be operative since single or multiple ventricular pacemakers rarely fibrillate a heart at normal body temperature.

Another possibility to consider is the presence of an area of persistent depolarization in the ventricle. Marked cooling has been reported to prevent repolarization of Purkinje fibers[1] and is known to cause a partial loss of resting potential in most, if not all, cardiac fibers.[5] Also, the demonstration by Hegnauer of a decrease in accommodation in hypothermic heart muscle suggests that the cooled heart would be more likely to fire repeatedly in the presence of a persistent depolarization. However, it seems unlikely, in terms of studies of single fibers in isolated preparations, that at the temperatures associated with the highest incidence of ventricular fibrillation there would be either a marked loss of normal resting potential or a failure of certain fibers to repolarize.

The third major possibility mentioned as a predisposing factor is the disorganization of the spread of activity in the ventricle. This mechanism is particularly attractive because of the different electrophysiological properties of ventricular muscle and Purkinje fibers. However, several groups of investigators have shown that the effect of lowered temperature on the repolarization of ventricular muscle fibers and Purkinje fibers is quite similar.[5] Action potentials from both tissues are prolonged to a comparable extent by cooling, especially when the frequency of contraction remains between 30 to 50 beats/min. Moreover, Hegnauer's recent studies have shown that the conduction velocity in both ventricular muscle and specialized tissue changes to a comparable extent during hypothermia. A differential effect of temperature on either refractoriness or conduction in ventricular muscle and specialized fibers thus appears less likely to be the major factor in the cause of fibrillation.

In spite of this attempt to eliminate most of the apparent causes of fibrillation during hypothermia, it is not surprising that the cooled heart is highly susceptible to this particular arrhythmia. If we consider all of the changes in electric activity caused by cooling it is apparent that each one predisposes either to multiple firing, local blocks, or reentry. The studies of hypothermia reported today have shown a decrease in accommodation, a marked prolongation of the relative refractory period, a lesser prolongation of the functional refractory period, and no marked change in threshold. If we consider the transmembrane potentials of the single cardiac fiber the effect of these changes is readily apparent. Under conditions of hypothermia the transmembrane potential changes slowly during repolarization and thus, for a considerable period of time, the membrane potential is close to the threshold potential. Because of the decrease in accommodation, repetitive firing, similar to that caused in skeletal muscle by Prostigmin, or veratrine, is quite likely to take place. Because the functional refractory period is much shorter than the total refractory period, action potentials arising from such repetitive firing would show a decreased amplitude and rising velocity. Such action potentials will propagate at reduced velocity and have a greatly decreased safety factor. Also, because of their prematurity, these action potentials may fail to enter the specialized conducting system or will do so only after a marked delay in the junctional area.[6] Under conditions such as these, the appearance of disorganization, local block, and reentry is to be expected.

One additional observation should be considered. It has been shown that an increase in the extracellular concentration of calcium is very likely to initiate fibrillation of the hypothermic heart.[7] One important effect of calcium is to increase the responsiveness, in terms of rise velocity and amplitude of the action potential, of the partially depolarized membrane.[8] It appears that increased vulnerability of the cooled heart to fibrillation may result because, in the presence of excess calcium, responses may be initiated at an even lower level of membrane potential and thus cause an additional shortening of the functional refractory period.

In summary, it is not surprising that the cooled heart fibrillates either spontaneously or in response to extrinsic stimuli. Studies of the excitability of the intact heart during hypothermia and of the transmembrane potentials of single fibers in isolated preparations of cardiac muscle have provided a number of suggestions concerning the possible cause and mechanism of this arrhythmia. Demonstration of the actual causes and mechanisms probably will come from studies of the electric activity of single fibers of ventricle and specialized conducting system in the intact heart *in situ*.

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INFLUENCE OF PHARMACOLOGICAL AGENTS ON SPONTANEOUS AND SURGICALLY INDUCED HYPOTHERMIC VENTRICULAR FIBRILLATION*

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The results of the studies on ventricular excitability and refractoriness presented elsewhere in this monograph[1] suggest that ventricular fibrillation (VF) under hypothermia is associated with a certain set of electrophysiological conditions of the myocardium that differ in many respects from those found in other conditions associated with arrhythmias and VF.[2] Therefore, it might be anticipated that the pharmacological control of VF under hypothermia may present somewhat different problems. This expectation has been substantiated experimentally.[3]

At present, our state of knowledge of the fundamental mechanisms involved in the development and establishment of VF is too limited to permit a direct evaluation of the pharmacological properties that are responsible for antiarrhythmic activity. Thus, until such time as a direct approach becomes possible, evaluation of antiarrhythmic agents can be based only on empirical criteria. It is therefore mandatory that the activity of antiarrhythmics, in relation to hypothermic VF, be assessed only under experimental conditions that simulate as closely as possible the actual conditions that may obtain in human use.

It is generally well appreciated that, if the development of VF is prevented in the hypothermic man, his tolerance to low body temperatures may be greatly increased. Furthermore, when VF ceases to be a major complication, the advantages of low body temperature with the associated low metabolic rate may find greater use in medicine and surgery.

From a pharmacological point of view, the susceptibility of the hypothermic ventricle to fibrillation provides an experimental opportunity for the study of antiarrhythmic compounds. Although several experimental methods have been employed in the evaluation of antiarrhythmic activity, it is unlikely that any single method can assess all the factors that may be involved in the development of this complex phenomenon under different conditions.[4]

From yet another point of view, study of the changes in the electrophysiological properties brought about by effective compounds may provide valuable clues as to the fundamental mechanisms that play a dominant role.

This paper is a review of studies, mostly empirical, carried out in our laboratory with a variety of compounds over the last three years in attempts to delineate active agents. Since detailed results of parts of these studies are published elsewhere,[3, 5-7] only the key findings will be discussed.

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Methods

Two experimental methods have been used in our laboratory in the evaluation of antiarrhythmic agents under hypothermia. In one method, antiarrhythmics were evaluated in relation to protection against VF occurring *spontaneously* in progressively cooled animals; in the other method, antiarrhythmics were tested for an effect on incidence of VF occurring in animals subjected to experimental ventriculotomy at moderate hypothermic temperatures. In both cases drugs were injected intravenously when the heart temperature of 27° C. was reached. Further details of each method will be found elsewhere.[3, 5-7] There is at present considerable evidence to suggest that, in each of these experimental methods, different factors are involved and that the two terminal conditions, although apparently similar, may not be entirely comparable.

Controls

In the experiments on spontaneous VF, dogs were anesthetized with pentobarbital and were cooled to terminus in a cold-water bath. All animals were allowed to respire spontaneously until a heart temperature of 26° C. was reached. During that period, they become moderately acidotic, as is well known.[8] Artificial respiration was used at lower temperatures in order to prevent the complication of respiratory arrest. These experimental conditions were chosen purposely because they are associated with a high incidence of spontaneous VF in untreated animals. Terminal cardiac activity and terminal heart temperatures served as the important experimental criteria.

Over 150 control animals used in groups of 10 or 20 gave incidences of VF ranging from 70 to 90 per cent.* The results from more than 100 animals analyzed are shown in FIGURE 1. VF is the predominant mode of death at the higher temperatures (24 to 20° C.) while cardiac arrest accounts principally for mortality at low temperatures (17 to 15° C.). Nevertheless lethal temperatures form a continuous spectrum, and the logarithms of these values show a statistically normal distribution.[6] Thus the median lethal temperature of the large group was found to be 20.1 ± 0.7° C. In small groups of 10 to 20 control animals the mean lethal temperatures vary from 19.5° to 20.5° C. A similar range is also applicable for the median (as calculated from cumulative mortality curves),[6] although the two are not identical since the former is influenced by a few extreme values that have little influence on the latter.

In experiments using the surgical approach, right ventriculotomy and ventriculography were performed under hypothermia during venous inflow occlusions. Subsequently, the surviving animals were rewarmed. In this group of tests, all the animals were artificially respired from the onset of cooling so as to avoid shifts of blood *p*H during that period. These conditions were set to simulate the clinical counterpart. The incidence of VF in control groups at different heart temperatures and with different anesthetics is shown in FIGURE 2. Although the incidence of VF depends somewhat on the anesthetic, it seems to be due predominantly to cold and does not appear to vary greatly in the range from 30° to 20° C.

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* In this classification, all animals in which the ventricle exhibited fibrillation as the final terminal event are classified under VF.[3] The previously proposed distinction of asystolic fibrillation[9] has been abandoned.[3, 6]

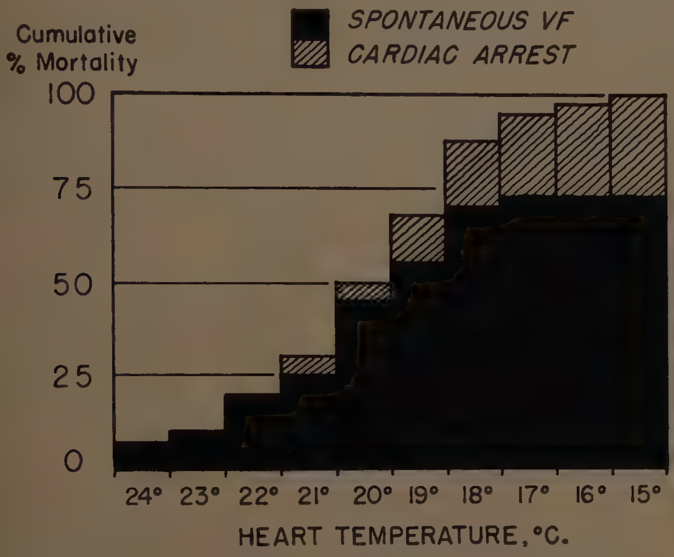

FIGURE 1. Controls. Progressive cooling to terminus.

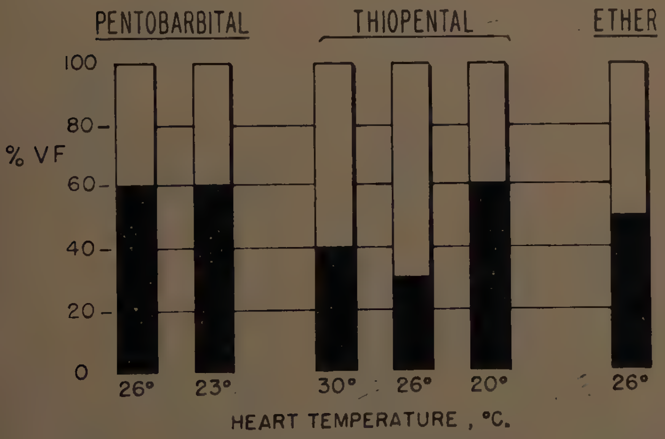

FIGURE 2. Controls. Ventriculotomy under hypothermia with controlled blood pH.

In all the pharmacological experiments and their controls pentobarbital was used as the anesthetic, and surgery was performed at 26 ± 1° C. during a 15-min. venous inflow occlusion. In more than 80 control animals used in groups of 10 to 20 the incidence of VF varied between 50 and 70 per cent.

These studies on controls, most of which were made concurrently with and under the same conditions as the treated animals, provide reliable criteria for the assessment of pharmacological protection.

Quinidine

Study of the action of this classic antiarrhythmic on hypothermic VF appears to have been neglected. This may be due partly to a widespread but mistaken notion that this compound is effective only in atrial arrhythmias. Both experimental and clinical facts suggest otherwise.[10]

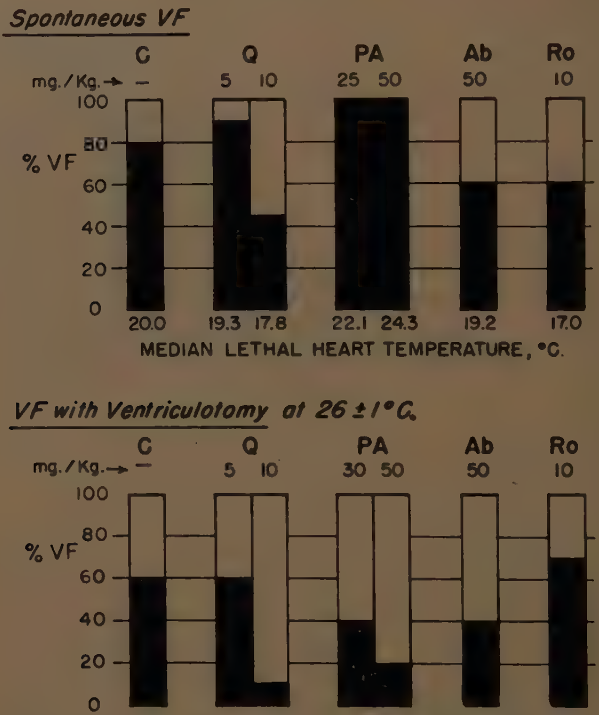

FIGURE 3. Antiarrhythmics. Key: C, controls; Q, quinidine; PA, procaine amide; Ab, Ambonestyl; Ro, Ro 2 7302.

In progressive hypothermia quinidine afforded a significant protection against spontaneous VF (FIGURE 3). The relatively large doses required are within the therapeutic range. In treated animals protection from VF prevented deaths at higher temperatures and resulted in an over-all decrease in the lethal temperature of the group (FIGURE 3). This is interpreted as evidence that the effect of the drug is fairly specific. Purely depressant agents (such as KCl) may prevent VF, but at the same time cause early death at high temperatures.

Under experimental ventriculotomy at 26° C., the larger doses of quinidine provide a significant protection, as shown in FIGURE 3. These results were obtained in animals maintained under controlled ventilation throughout cooling as described under *Methods*. When quinidine was tested in animals that were allowed to respire spontaneously during cooling (thereby becoming mildly acidotic), the degree of protection following ventriculotomy was minimal (see TABLE 2 and *p*H discussion). This emphasizes the importance of *p*H regulation in conjunction with pharmacological treatment. The beneficial effects of the former alone are well known.[8]

Encouraging as these results may be, the use of quinidine in the prevention of VF during experimental surgery is limited by the observation that if the period of inflow occlusion is prolonged beyond 10 min., the myocardium becomes progressively hypotonic and incapable of producing adequate tensions. Death of the animal from acute heart failure follows unless other measures are taken. This condition will be discussed more fully below.

It is rather surprising that these experiments constitute the first conclusive demonstration of the effect of this compound in hypothermia under controlled experimental conditions.[11] Insofar as we are aware, its value in human hypothermia has not been determined.

Procaine Amide

In contrast to quinidine, this compound did not exhibit any protective effect against spontaneous hypothermic VF in doses ranging from 25 to 50 mg./kg. Animals treated with the larger doses had a tendency to fibrillate at temperatures higher than those of the controls (FIGURE 3). The doses employed were similar to those used by others to demonstrate the effect of this compound in the dog on other experimental arrhythmias.[12] In any event, smaller doses had no significant effect under hypothermia.

These findings would seem to preclude the use of procaine amide in experimental cardiotomy at 26° C. since some of the treated animals may fibrillate spontaneously before this temperature is reached. However, experiments were made and it was found unexpectedly that most treated animals that reached the desired temperature underwent ventriculotomy without developing VF. The results are difficult to interpret since a few animals developed spontaneous VF prior to surgery. Nevertheless, even when the total incidence of VF is considered, as shown in FIGURE 3, a protective effect is apparent. What is perhaps more important is that none of the animals that underwent surgery developed the condition of acute heart failure seen with quinidine.

Reports on the effect of procaine amide under hypothermia appear to be contradictory. Several investigators found no beneficial effect,[13, 14] while others claimed a very significant protection.[15, 16] The present results are in agreement with both conclusions. As shown here, the difference lies in the methods and temperatures used in the evaluation.

The divergent effect of procaine amide under hypothermia is one of several findings suggesting that protection from spontaneous and surgically induced VF is not dependent on a single set of factors. In contrast to quinidine, procaine amide seems to protect against the development of VF at relatively high temperatures even in the presence of a strong extrinsic stimulus. I does not, however, prevent VF from occurring spontaneously at somewha lower temperatures and may even set conditions that favor the developmen of spontaneous VF with further cooling. In the latter case the undesirabl action of procaine amide seems to be additive to the detrimental effect o cold. This probably is due to an action on myocardial conduction, sinc both cold and procaine amide are known to prolong conduction in the myocardium[17, 18] an effect that may be responsible for spontaneous hypothermi VF.[1, 2] This suggestion is supported by observations on hypothermi animals treated with certain local anesthetics (TABLE 1) that also exhibite a tendency to develop VF at temperatures higher than those of the controls.

Digitalis

To complete the study of the well-known cardiac drugs, the effects o digitalization on hypothermic VF were determined.[19] Digitalization wit

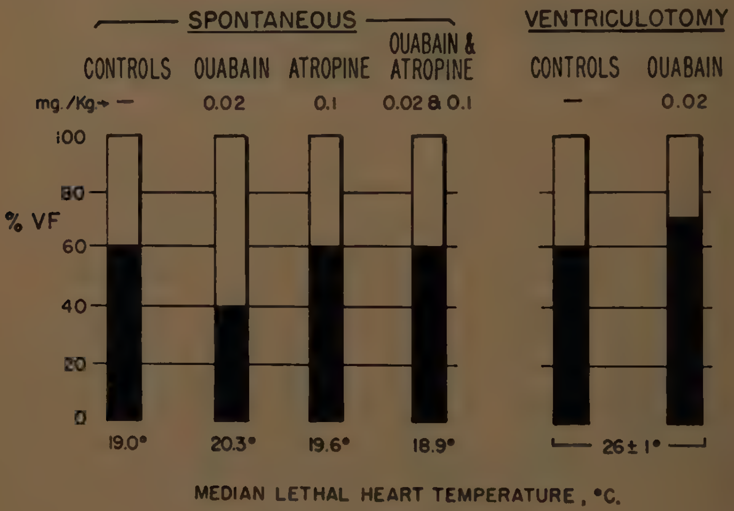

FIGURE 4. Digitalization.

full doses of ouabain did not appear to alter the incidence of spontaneous VF but the treated animals had a tendency to terminate in cardiac standstill a relatively high temperatures (FIGURE 4). This condition differed from tha seen at very low temperatures or with depressant drugs in that, in the latte the ventricles are not responsive to direct electric stimulation. By contrast the ventricles of digitalized animals terminating in standstill were responsiv to direct electric stimulation with restoration of cardiovascular dynamic In general, this undesirable effect of ouabain was obviated by prior treatment with atropine (FIGURE 4) and therefore may be attributed to the well-known vagomimetic effects of the drug.

In experimental ventriculotomy under hypothermia, ouabain again ha no significant effect on the incidence of VF that was similar to that of the controls (FIGURE 4). The over-all results, if applicable to man, would suggest that digitalization is not a contraindication to hypothermic surgery.

The influence of digitalization on hypothermic VF was studied chiefly in an attempt to correlate the findings with previous results showing an extreme sensitivity of the hypothermic myocardium to exogenous calcium.[20] However, the results suggest no such correlation, since digitalization had no significant effect on the susceptibility of the hypothermic heart to VF. Other experiments[19] showed that digitalis toxicity is reduced at hypothermic temperatures. In view of the previous findings with calcium, these results with ouabain do not support the well-known hypothesis of calcium-digitalis synagonism.

Screening Tests

In addition to quinidine, procaine amide, and ouabain, more than thirty compounds were evaluated for antifibrillatory activity in spontaneous hypothermic VF. Selection was based on previous reports indicating antiarrhythmic activity when tested on other experimental preparations. A few were experimental compounds newly developed as antiarrhythmics. The remainder were known pharmacological agents that previously had been found to possess antiarrhythmic properties by a number of investigators using a variety of methods. The latter group included local anesthetic, antimalarial, anticholinergic, and antihistaminic compounds. A partial list is given in TABLE 1. Detailed results and methods are published elsewhere.[3] All agents were injected intravenously when the heart temperature reached 27° C.

TABLE 1

PHARMACOLOGICAL AGENTS* SCREENED FOR ANTIARRHYTHMIC ACTIVITY UNDER HYPOTHERMIA

Antimalarials
- Chloroguanide
- Chloroquine
- Pamaquine
- Pentaquine
- Primaquine
- Quinacrine

Local anesthetics
- Dibucaine
- Lidocaine
- Procaine
- Petracaine

Antihistaminics
- †Antazodine
- †Antergan
- †Chloromethapyrilene
- Chlorophenpyridamine
- Diphenhydramine
- †Doxylamine
- †Methapyrilene
- Phenindamine
- Pyranisamine
- Thonzylamine
- Tripelennamine

* Partial list.
† Accepted for further testing.

From the results of the screening experiments, seven compounds were selected for further testing. The remainder were rejected, since the screening tests indicated that the probability that any of these compounds would have an appreciable effect[3] was extremely small (1:1000 or less). The selected agents were subjected to further testing using larger groups of animals in several more elaborate experiments, the results of which will be presented. Selection of compounds for inclusion in the experiments involving surgery under hypothermia was based only in part on these screening tests. Several compounds that were of specific interest, such as some of the new antiarrhythmics, were evaluated in this latter preparation even though the screening experiments indicated lack of activity in relation to spontaneous VF.

New Antiarrhythmics

The tests with new compounds included the procaine amide analogue Ambonestyl* (MC 4112), several diethyl amides (SC 2919, SC 3323, SC 3412, SC 3920)†, and certain steroidlike compounds (Ro 2 5803, Ro 2 7302)‡. Although some of these compounds could be rejected on the basis of the screening tests, more extensive studies were made with the most promising of them because of pharmacological interest.

Results of these more extensive tests with Ambonestyl and Ro 2 7302 are shown in FIGURE 3. Larger doses than those shown were within the toxic range, and were not tested. Neither of these compounds had an activity superior to that of quinidine in either spontaneous or surgically induced hypothermic VF.

Interest in Ambonestyl was aroused by previous reports that this compound may be very effective in hypothermic VF under surgery.[21] The present results and other recent reports indicate that this effect is not very striking.[22, 23] In hypothermic ventriculotomy, the antifibrillatory effect of Ambonestyl is not superior to that observed with procaine amide although Ambonestyl, unlike procaine amide, does not precipitate spontaneous VF under hypothermia. The latter differences may be related to the rather weak local anesthetic activity of Ambonestyl when compared with that of procaine amide[18] for the reasons previously discussed.

In general, these experimental results on Ambonestyl are more in agreement with findings of clinical trials with this drug under normothermic conditions.[24] What is not generally appreciated is the fact that Ambonestyl, although perhaps less potent than procaine amide, is considerably more specific, mainly because of its less prominent anesthetic activity.[18] Specificity may be most desirable under certain conditions, as in the case of hypothermia. If compounds can be developed that have the potency of procaine amide and the specificity of Ambonestyl, they will have extensive therapeutic potentialities. For this to be accomplished, however, there is a need for revision of the methods currently used for screening and evaluating antiarrhythmic activity, which at present seem to depend mainly on the ability of the compound to alter the conductive properties of the myocardium.

Several of the SC compounds were tested on the surgical preparation. At doses of 5 mg./kg., these compounds did not alter the control incidence of VF. In larger doses (10 mg./kg.) the complication of acute heart failure developed with these drugs as with quinidine. Therefore, tests have been discontinued until more information becomes available from other studies on this condition (see below).

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* E. R. Squibb.

† G. D. Searle & Co.

‡ Hoffman-La Roche, Inc.

Antihistaminics

Early screening tests suggested that some of these compounds might prove effective as hypothermic antiarrhythmics,[25] and the group so screened therefore was enlarged to include those listed in TABLE 1. Compounds not rejected in the screening tests were retested in larger groups of animals and at several dose levels.[3, 20] The results are given in FIGURE 5, where comparisons may be made with controls and with quinidine-treated animals. Against spontaneous VF several compounds displayed greater potency than quinidine, the most potent of these being antazoline, followed by chloromethapyrilene and methapyrilene. Doxylamine and Antergan possessed potencies about equal to that of quinidine. The comparisons may be made in several ways:[3] (1) the lethal temperatures of each group may be compared, using cumulative mortality lines from which the median lethal temperatures (LT_{50}s) are obtained, and (2) the dose-response curves may be compared to that of quinidine in respect both to VF and LT_{50}. For these compounds, as for quinidine, suppression of VF results in a lowering of the LT_{50}, which argues for the specificity of the pharmacological action. However, the degree of

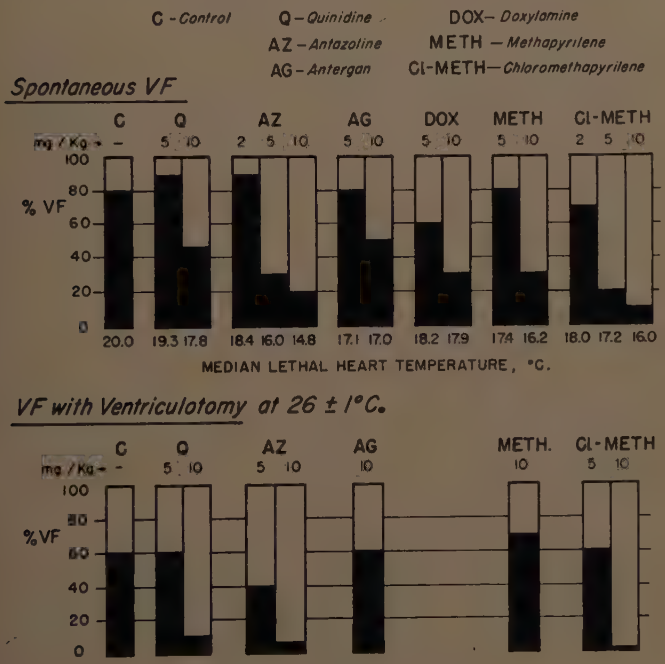

FIGURE 5. Antihistaminics.

specificity varies among the several effective compounds, as revealed in the varying degrees to which the LT_{50} is lowered through suppression of VF.[3]

It is apparent also from FIGURE 5 that some compounds that are effective against spontaneous VF are not necessarily effective against the VF induced by cardiotomy. This again appears to demonstrate a pharmacological difference between the two conditions. Certain other antihistaminics displayed marked protection during cardiac surgery. However, as with quinidine, protection in this case was associated with a high incidence of acute heart failure when venous occlusion exceeded 5 to 7 min. This was most striking with antazoline, but could be combated by prior digitalization.

The obvious question raised by these results is whether the antifibrillatory activity of the effective antihistaminics is related to any of the other known properties of this group of compounds (for example, antihistaminic, local anesthetic, anticholinergic, antiveratrinic). No such correlation is revealed from a comparison of the most effective compounds with those whose activity was not detectable in the screening tests (TABLE 1). Among the ineffective compounds are several with potent antihistaminic, anticholinergic, and loca anesthetic properties. It is also striking that the most effective agents have no other common characteristics other than the obvious chemical similarity of the two methapyrilenes and the fact that all of these agents were developed as antihistaminics. In addition, no correlation could be established between activity in this experimental test and that found in other experimenta preparations employed for evaluation of antiarrhythmic potency, although the same group of compounds was not tested in all instances. The latter finding is not surprising, since there are many reasons for accepting the postulate that hypothermia represents a somewhat specific condition. The evaluation of antifibrillatory activity under this condition appears to be more severe and perhaps more selective.

Role of pH

Of some theoretical interest are results of cardiac surgery performed on animals that were not respired and therefore become moderately acidotic during the period of cooling. When ventriculotomy is performed on such preparations at 26° C., invariably 100 per cent of the control animals develop VF on incision (TABLE 2). Treatment with quinidine has only a small effect, while treatment with Ambonestyl reduces the incidence to 50 per cent When these results are compared with the effect of the same drugs on spontaneous VF (where all the animals are allowed to breathe spontaneously and therefore become moderately acidotic during early cooling) certain interesting relationships become apparent.[3, 11] Quinidine seems to act primarily in preventing spontaneous VF, while Ambonestyl has an equal effect on both spontaneous and surgically induced VF. Furthermore, *p*H changes seem to play an insignificant role in the action of Ambonestyl while having a distinct effect on that of quinidine. With uncontrolled respiration, quinidine appears to act as a general antiarrhythmic, preventing the development of spontaneous ectopic activity and thus, indirectly, fibrillation; when ectopic extrasystoles are induced, as during cardiotomy, the degree of protection is far less. By contrast, Ambonestyl provides the same protection in the presence or absence of surgically induced ectopic activity and thus has a similar effect on the incidence of either spontaneous or surgical VF. In this respect, Ambonestyl may be said to act mainly as an "antifibrillatory" agent.

Under hypothermia, *p*H control alone has a distinct antiarrhythmic action as shown by the findings on both spontaneous and surgically induced VF.[8, 11, 21] An antifibrillatory effect of quinidine can be demonstrated clearly only when *p*H control is maintained. Whether these considerations can be extended to other compounds or are generally applicable remains to be demonstrated. At present they stand only as tentative, working hypotheses.

TABLE 2
CONTROL OF BLOOD *p*H AND ANTIARRHYTHMIC ACTIVITY UNDER HYPOTHERMIA

	Controls	Quinidine	Ambonestyl
Spontaneous VF			
Uncontrolled *p*H..........	80	10	40
Controlled *p*H............	10	—	—
VF with ventriculotomy			
Uncontrolled *p*H..........	100	80	50
Controlled *p*H............	60	10	40

Heart Failure During Surgery

As shown above, animals subjected to cardiotomy during inflow occlusion at 26 ± 1° C. could be protected from VF by previous treatment with quinidine or certain of the antihistaminics. However, under these conditions, a large proportion of the treated animals developed an atonic myocardium, with production of obviously ineffective contractions.[7] This could be ascertained by gross observation of the exposed heart. As venous return is re-established at the end of the procedure, the hypotonic myocardium cannot maintain a significant cardiac output, and a profound hypotension is established (less than 30 mm./Hg). Insofar as it can be determined at the present time, the hypotonic condition does not appear to develop until about 8 to 12 min. after inflow occlusion. In fact, if the period of inflow occlusion is limited to 5 min., the hypotonic state is not manifested. The development of this condition of acute heart failure is fatal unless otherwise treated. In a few cases animals with marked hypotension could be rewarmed with some improvement in their cardiovascular status, but it is very unlikely that prolonged survival could be established.

This sequence of events, although it occurs frequently in animals treated with antiarrhythmics, is not peculiar to this group. A similar condition develops in a very large proportion of controls and in treated animals that fibrillate during the procedure, but that have been defibrillated by electric countershock. Thus, it is possible that the high proportion of acute heart failures seen in the drug-treated animals could be due to the unmasking of an effect not manifested in untreated animals due to the development of VF early in the procedure. It appears unlikely that the drugs actually precipitate the acute failure, since this condition does not develop if the occlusion time is limited to 5 min. However, the possibility can not be excluded that the drugs may act as additive factors. The relationship between incipient heart failure and VF is at present a matter of conjecture. In any event, development of acute failure is rather uncommon in control animals that do not develop VF during the surgical procedure. Current work in our laboratory[26] indicates that acute heart failure is preventable by previous digitalization and can be readily reversed by the administration of epinephrine and cardiac massage. A complete evaluation of this condition remains a subject for future investigation.

Electric Defibrillation

Pharmacological control of VF during hypothermic surgery may appear superfluous from a practical point of view if defibrillation with electric shock can be readily accomplished either during or at the end of the procedure. It has been claimed, however, that hypothermic hearts are difficult to defibrillate with electric shock;[27] therefore it has been accepted that under clinical conditions rapid rewarming should be performed before attempts at defibrillation are made. These conclusions were said to be based on experimental evidence from studies on dogs. Our results are somewhat at variance with these statements and do not support such a generalized conclusion.

In more than 100 experiments, it was found that, in the range of 28° to 23° C., the hypothermic heart of the dog was readily defibrillated with single electric shocks, and that many repeated fibrillations and defibrillations could be produced on the same animals without any difficulty.[28] In these experiments, fibrillation was produced either by electric stimuli or by surgical procedures such as ventriculotomy, digital exploration of the myocardium, and ventriculography. In these surgical tests, the period of inflow occlusion was limited to 5 min. By contrast, fibrillation, which occurs spontaneously during progressive cooling at lower temperatures (22° to 18° C.), becomes much more difficult to handle, chiefly because of the development of an atonic unresponsive myocardium even though the fibrillatory activity can be arrested readily. A similar difficulty may arise when VF occurs in animals treated with antiarrhythmics if they developed a hypotonic myocardium. In this case, also, the principal difficulty seems to be the hypotonia. If the latter is treated with inotropic agents, permanent defibrillation and resuscitation of the animal are readily accomplished.[26]

It appears, therefore, that as long as the heart is in functionally good condition regarding myocardial contractility, defibrillation with electric countershock is very successful under hypothermia, and often fewer trials are needed than under normothermia. However if, for any reason, myocardial contractility is impaired, resuscitation of the fibrillating heart by electric shock alone becomes difficult and often impossible. The fact that such hypotonic hearts are difficult to resuscitate after fibrillation is generally well known,[29] and it does not appear to be peculiar to hypothermia. To what extent deep hypothermia (below 20° C.) per se affects the functional state of the myocardium, especially when combined with anesthetics and other drugs, remains to be determined.

Summary

Two tests were employed for the evaluation of antiarrhythmic activity under hypothermia: one against spontaneous ventricular fibrillation (VF) during progressive cooling, and the other against VF occurring during ventriculotomy at 26° C. Results indicate that activity in each of these 2 tests may depend on different pharmacological effects.

More than thirty compounds (including old and new antiarrhythmics, local anesthetics, antimalarials and antihistaminics) were screened. Nine selected compounds were subjected to further testing.

Quinidine is effective in preventing spontaneous VF and lowering lethal temperatures. The most promising of the new antiarrhythmics (Ro 2 7302 and Ambonestyl) were less effective than quinidine. Among the antihistaminics, antazoline, chloromethapyrilene, and methapyrilene were more effective than quinidine, while doxylamine and Antergan were about as effective as the latter. Many other antihistaminics and several local anesthetics and antimalarials had no detectable activity. Procaine amide and certain local anesthetics increased the incidence of VF at relatively high temperatures. This may be attributed to an additive effect between these agents and cold on myocardial conductivity.

In experimental ventriculotomy under hypothermia with controlled blood *p*H, quinidine, antazoline, and chloromethapyrilene had a definite antifibrillatory effect. Over-all survival was limited by the development of acute heart failure in many treated animals that escaped VF. A similar status often developed following electric defibrillation of control or treated animals. In general, this condition was found to respond to treatment with inotropic agents.

As a working hypothesis, a distinction is made between antiarrhythmic agents that prevent VF indirectly by inhibiting ectopic activity and antifibrillatory agents that prevent VF in the presence of spontaneous or induced ectopic activity. Quinidine acts chiefly as an antiarrhythmic. Its antifibrillatory effect is manifested only when hypothermic acidosis is not allowed to develop. By contrast, Ambonestyl and, at high temperatures, procaine amide act mainly as antifibrillatory agents.

Ouabain did not alter the incidence of hypothermic VF occurring spontaneously or during ventriculotomy. Thus, digitalization does not appear to be a contraindication to hypothermic surgery.

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CARDIODYNAMICS AND THE CORONARY CIRCULATION IN HYPOTHERMIA

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On the basis of early studies, certain investigators[1, 2] postulated that death rom hypothermia occurred as a result of cardiac failure, possibly secondary o an impaired coronary blood flow. The findings of low arterial pressure, lightly elevated venous pressure, prolongation of myocardial contraction, ncreased blood viscosity, and high incidence of ventricular fibrillation sup-orted this hypothesis. However, within the past few years sufficient quan-itative data have accrued to permit a definitive statement concerning the unctional status of the myocardium in hypothermia. Consideration of these uantitative data, as well as the influence of hypothermia on coronary blood low, forms the basis of this report.

Functional Status of the Myocardium in Hypothermia

The function of the myocardium in hypothermia has been evaluated by (1) study of pressure pulse contours, (2) determination of cardiac work per-ormance and efficiency, and (3) direct measurements of the contractile orce of the heart.

Pressure pulse contours. In the pressure pulse contour method the prin-ipal criteria for evaluating cardiac function are (1) the rate of ventricular pressure increase at the onset of systole, (2) the duration of the ejection phase, and (3) the initial tension or end-diastolic pressure. FIGURE 1 depicts rec-ords of pressure pulses simultaneously obtained from the aorta, left ventricle, and left atrium of the open-chest dog during the development of immersion hypothermia.[3] Despite the marked bradycardia produced by hypothermia and the prolongation of the contraction phase of the cardiac cycle, the initial lope of the ventricular pressure curve was not greatly prolonged by hypo-thermia. Isometric contraction increased from a control value of 0.06 sec. (record A) to 0.08 sec. at 23° C. (record F) and to 0.10 sec. at 20.5° C. (record H). The ejection phase of the cardiac cycle increased from 0.14 sec. at 40° C. to 0.90 sec. at 20.5° C.* Initial tension did not increase until severe hypo-thermia was produced, at which time it was increased only by about 2 mm. of mercury (records G and H). The failing heart is characterized by a pro-ongation of isometric contraction, an abbreviation of ejection, and an increase of initial tension in the presence of a decrease in magnitude and duration of ventricular contraction. However, the minimal increases in isometric contraction and initial tension observed in terminal hypothermia are not considered to be sufficiently large to indicate cardiac failure. Fu thermore, at 23° C. no increase in initial tension and a barely perceptib prolongation of isometric contraction occurred. The characteristics of failing heart, however, may be induced in hypothermia by increasing hea

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* The lengthening of the ejection phase of the cardiac cycle with reduction in body temperature cannot be used as evidence that cardiac failure does not occur, since a short-ening of ejection due to myocardial failure might be masked by the direct effect of cold on the contraction process. However, at any given temperature, changes in ejection time would be a valid means of estimating cardiac performance.

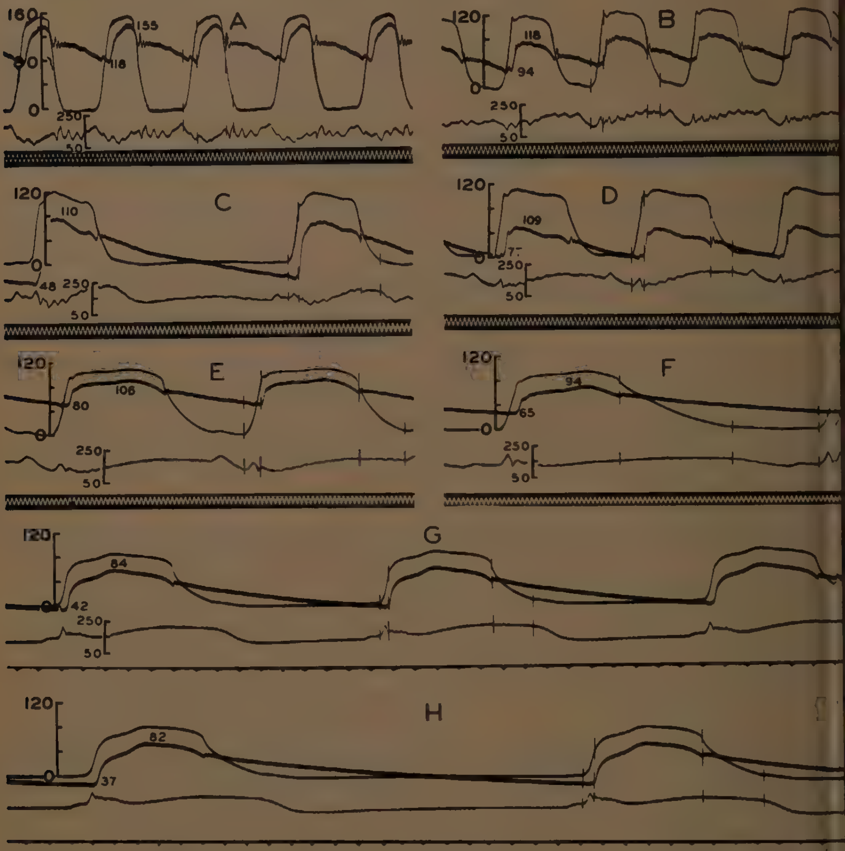

FIGURE 1. Effect of hypothermia on ventricular (*upper curve*), aortic (*middle cu* with incisura), and left atrial pressure pulses. Record A, 40° C., heart rate 158; record 33.5° C., heart rate 142; record C, 33.5° C., heart rate 53 (peripheral right vagus ne stimulation); record D 27.5° C., heart rate 100; record E, 26° C., heart rate 71; record 23° C., heart rate 43; record G, 22° C., heart rate 21; record H, 20.5° C., heart rate Ventricular and aortic pressures in mm. Hg. Left atrial pressure in mm. saline. Ti scale records A through F, 0.02 sec.; records G and H, 0.20 sec. Reproduced by permiss from *Circulation Research*.[3]

rate by means of stimulation of the left atrial appendage. In FIGURE 2 presented records taken when the blood temperature had reached 20° In record A the heart rate was 16 beats/min. Increasing the rate by elect stimulation to 34 beats/min. (record B) induced an improvement in card function, since aortic and left ventricular pressures increased and left atr ressure decreased slightly. A further increase in heart rate to 43 beats/min. ecord C) tended to restore the pressures toward the control values found in ecord A. However, an increase in heart rate to 57 beats/min. (record D) esulted in a dramatic fall in left ventricular and aortic pressures and a rise

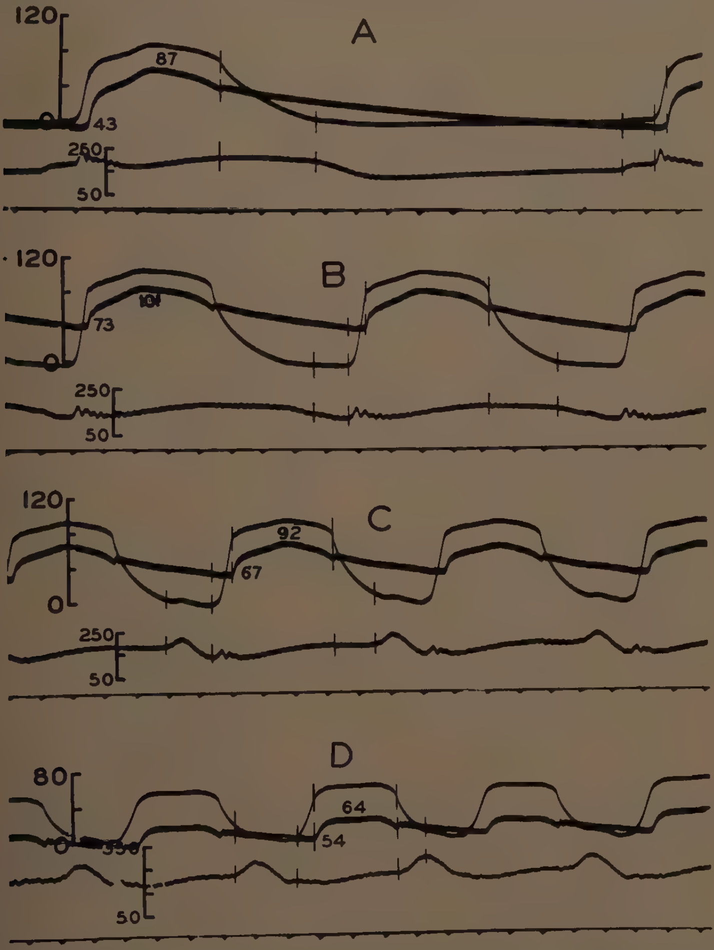

FIGURE 2. Effect of progressive increase in heart rate by electric stimulation of the trial appendage at a temperature of 20° C. From top to bottom in each record, ventricuar pressure, aortic pressure (with incisura), and left atrial pressure. Ventricular and ortic pressure in mm. Hg. Left atrial pressure in mm. saline. Time scale, 0.20 sec. Reproduced by permission from *Circulation Research.*[3]

n left atrial and end-diastolic pressures. Associated with these pressure hanges were an increase in the duration of isometric contraction and a lecrease in the duration of ejection. Thus, increasing heart rate to a point hat is considered bradycardia at normal temperature induces myocardial ailure in hypothermia. The signs of myocardial failure (record D, FIGURE 2) are due in large part to the onset of each systole prior to relaxation from th previous heartbeat, resulting in impaired ventricular filling. This, in tur produces a decrease in cardiac output and arterial pressure.

These studies of pressure pulses in hypothermia indicate that myocardi function is not impaired unless heart rate is increased by electric stimulatio

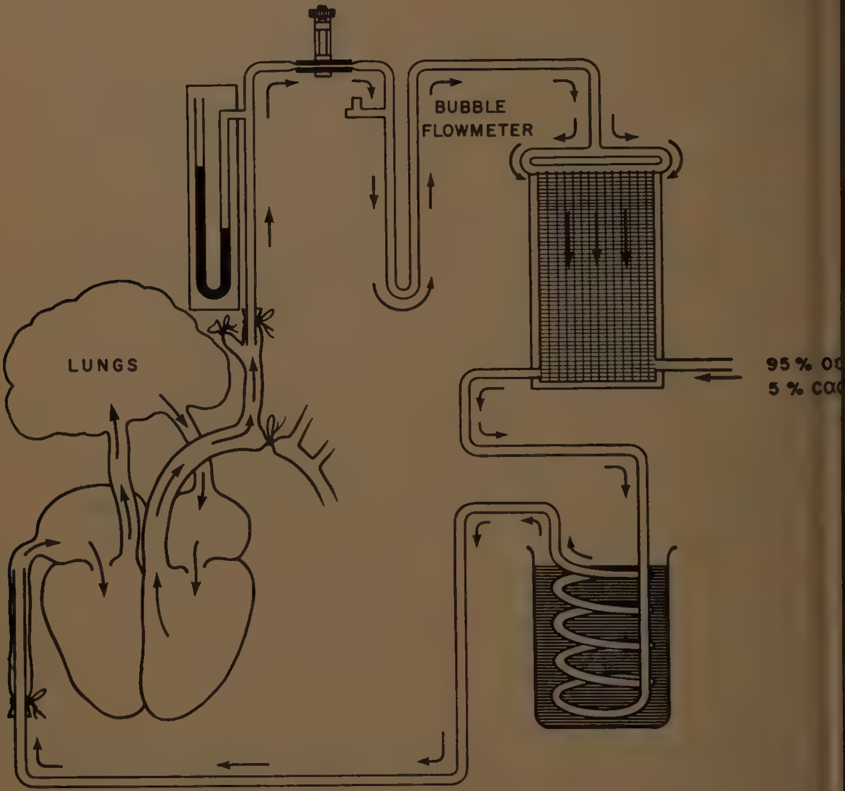

FIGURE 3. Schematic diagram of the rat heart-lung preparation.

Cardiac work performance and efficiency. A second method of assessin the functional status of the hypothermic heart is to compare its work pe formance and efficiency with that of the normothermic heart. Solomon an Sayers[4] of the Department of Physiology at Western Reserve Universi have used a heart-lung preparation in determining the effect of steroids the work capacity of the rat heart at 37° C. and at 32° C. A schemat diagram of the apparatus used in these experiments is shown in FIGURE 3. screen oxygenator was used in the system for oxygenating the blood an although blood perfused the lungs, the latter were not ventilated in the experiments. Blood from donor rats was obtained just prior to the expe ments, and a total volume of 50 ml. of blood was used in the system in ea experiment. In TABLE 1 are presented the results of these experimen

-I in column 1 refers to a heart-lung preparation of a rat with intact adrenals erfused with blood obtained from normal intact rats. I-A, on the other and, refers to the heart-lung preparation made from a normal intact rat, but erfused with blood obtained from rats adrenalectomized two or more weeks rior to the experiment and maintained on 1 per cent sodium chloride in their

TABLE 1

EFFECT OF STEROIDS ON CARDIAC WORK IN THE RAT HEART-LUNG PREPARATION

Preparation	Steroid added	Amount steroid added µg./100 ml.	LVWI gm./100 gm. ht.	
			37° C.	32° C.
I-I	0	0	254 ± 18 (9)	943 ± 93 (9)
I-A	0	0	86 ± 5 (7)	488 ± 37 (9)
I-A	B	2	111 ± 5 (7)	792 ± 78 (5)
I-A	B	10	224 ± 9 (7)	669 ± 18 (7)
I-A	B	50	79 ± 3 (5)	299 ± 30 (5)
I-A	B	500	38 ± 13 (5)	110 ± 13 (3)
I-A	T.H.F.	2	90 ± 7 (5)	432 ± 19 (4)
I-A	T.H.F.	10	96 ± 8 (5)	
I-A	T.H.F.	50	84 ± 6 (5)	
I-A	T.H.F.	500	45 ± 7 (5)	278 ± 22 (4)

Key: I-I, intact-intact (see text for definition); I-A, intact-adrenalectomized (see text or definition); LVWI, left ventricular work index (see text for definition). Numbers in arentheses refer to the number of experiments.

lrinking water up to the time of the experiment. LVWI refers to left ventricular work index. This is defined as mean arterial blood pressure × total olume of blood pumped (exclusive of the coronary blood flow) during an ntire experiment. In these experiments arterial pressure was set at 110 mm. f mercury and maintained at this level by adjustments of the screw clamp vhich served as peripheral resistance. The experiments were terminated vhen the hearts could no longer maintain this pressure in the face of maximal eripheral resistance. The work capacity of the intact rat heart perfused vith blood from intact rats was more than three times greater at 32° C. than t 37° C. (TABLE 1). In the preparation perfused with blood from adrenalecomized rats without added steroid a considerable reduction in work capacity

was noted at both 37° C. and 32° C., but the reduction in work capacity w
proportionately greater at 37° C. than at 32° C. Addition of corticosteron
(compound B) in a dose of 2 μg./100 ml. of blood increased work capaci
toward control levels at both 37° C. and 32° C., with a more marked effe
at the lower temperature. At a dose of 10 μg./100 ml. work capacity w
practically restored to control levels at 37° C., whereas in the preparatio
at 32° C. this dose was less effective than the 2-μg. dose in improving t
LVWI. Increasing the dose of corticosterone to 50 μg./100 ml. showed
definite depressant effect on work capacity at 32° C. Higher concentratio
of corticosterone were required to produce a toxic effect at 37° C. than
32° C. Addition of metabolically inert steroids such as tetrahydrocortis
(THF) had no enhancing effect on work capacity, and in high concentratio
exerted only a toxic effect.

McMillan *et al.*[5] have studied stroke work of the intact dog heart at 37°
and at 28° C. Cardiac output, heart rate, and aortic, pulmonic, and rig
and left atrial pressures were measured simultaneously during intermitte
intravenous infusions of blood. A plot of left ventricular stroke work again
left atrial pressure did not reveal a significant difference in ventricular fun
tion at the two temperatures, indicating no impairment of ventricular co
tractility in hypothermia. McMillan and his colleagues[5] also measur
coronary blood flow and found that, at comparable levels of work, the cor
nary blood flow was less during hypothermia, suggesting that the cool
heart was more efficient.

Cardiac efficiency at low temperatures was first studied by Evans[6] in 19
in the dog heart-lung preparation. With work load constant he observed
diminished oxygen consumption and increased mechanical efficiency wi
hypothermia. Recently, Badeer[7] and Reissmann and Van Citters[8] ha
confirmed Evan's work in the dog heart-lung preparation. However, in t
anesthetized intact dog, Edwards *et al.*[9] found a decrease in left ventricul
efficiency from 20.3 to 7.8 per cent with hypothermia. Although the obse
vations of Edwards *et al.*[9] in the intact dog appear at variance with tho
made in the heart-lung preparations, Reissmann and Van Citters[8] offer
reasonable explanation for these apparently divergent results. These inve
tigators[8] studied cardiac efficiency in the heart-lung preparation over a wi
range of cardiac work, at 37° C. and at 28° C. They noted that at any giv
work load the efficiency of the heart at 28° C. was significantly greater th
at 37° C. However, a marked reduction in cardiac efficiency occurred at t
lower work loads at both temperatures. Application of these data to t
intact dog indicates that comparisons of efficiency at normal temperatu
and high work loads with efficiency at low temperature and low work loa
may be misleading.

To what is the greater efficiency at low temperatures due? Is it due to t
decrease in heart rate alone, or to a specific effect of hypothermia? Bade
and Khachadurian[10] compared the efficiency of the hypothermic heart wi
that of the heart slowed to an equivalent rate by cooling the sinoatrial no
in the dog heart-lung preparation. Efficiency at normal temperatures w
found to increase slightly with reduction in heart rate, but the change w

t statistically significant. However, a similar reduction in heart rate pro- iced by hypothermia resulted in a significant increase in cardiac efficiency. om these data they concluded that the greater efficiency of the dog heart- ng preparation at lower temperatures is in large measure a result of the crease in temperature per se.

It has been postulated that a reduction in the basal oxygen requirements the heart is responsible for the increased efficiency at low temperatures.[8, 10] e have studied the oxygen consumption of the quiescent hypothermic art and, as might be expected, found it to be considerably reduced below

TABLE 2
OXYGEN CONSUMPTION OF THE NORMOTHERMIC AND HYPOTHERMIC POTASSIUM-ARRESTED HEART

No. xperiments	Coronary blood flow ml./min./100 gm. heart	Myocardial oxygen consumption ml./min./100 gm. heart		
		Beating heart 37° C.	K-arrested 37° C.	K-arrested 22° C.
15	73	9.18	2.08	0.66

at of the normothermic heart.[11] In these experiments, the aorta was cross- imped near its origin and the arterial system was supplied with blood at ° C. by means of a pump oxygenator.[12] The left coronary artery was rfused with blood shunted from the oxygenator through a rotameter[13] for w measurement and a glass coil for adjustments of coronary blood tem- rature to any desired level. Cardiac arrest was produced by continuous fusion of potassium chloride into the tubing leading to the cannulated ronary artery. Coronary blood flow was kept constant by adjustment of rfusion pressure, and blood samples for oxygen content were obtained from e coronary artery tubing and from the cannulated coronary sinus. Data m these experiments are summarized in TABLE 2. The values for oxygen nsumption for the potassium-arrested heart maintained at 37° C. are of e same order of magnitude as those reported by other investigators.[14-16] ie potassium-arrested heart, subjected to hypothermia, showed a consider- le reduction in oxygen consumption approximating one third that of the rmothermic arrested heart. To what extent this reduction in resting ygen consumption is responsible for the improved efficiency of the working art is difficult to say. Application of our data on oxygen consumption of e cold-arrested heart to the experimental results of Riessmann and Van tters[8] suggests that a significant portion of the difference in oxygen con- mption at 37° C. and 28° C. at a given work load could be accounted for the basis of a decrease in resting oxygen consumption, especially at the ver work loads where the difference in oxygen consumption at the two mperatures is small. It is quite possible that the balance of improvement of efficiency at lower temperatures could be due merely to the decrease heart rate. Although these calculations offer a reasonable explanation of th difference in efficiency at normal and low temperatures, they should be view with caution. First, the left ventricular temperature of the dogs in o experiments was about 22° C., whereas the heart-lung preparations of Reis mann and Van Citters were studied at 28° C. Furthermore, it is not know whether potassium influences myocardial oxygen consumption solely b abolishing myocardial contraction.

The experimental data obtained from intact and isolated hearts indica that in hypothermia cardiac work performance is equal to or greater than th of the normothermic heart, and cardiac efficiency is significantly increas at low temperatures.

Direct measurements of myocardial contractile force. A third meth employed in the evaluation of ventricular performance in hypothermia i the direct measurement of contractile force of the ventricles by means of strain gauge arch sutured to the ventricular wall. Goldberg[17] observed increase in contractile force of the right ventricle of the intact anesthetiz dog as body temperature was reduced. The increase in contractile fo was maximal between 24° C. and 31° C., and averaged 101 per cent abo control levels. In a similar experiment, Covino and Beavers[18] noted a thre fold increase in contractile force of the left ventricle with a reduction in te perature to 25° C. These authors[18] also observed the same effect in t isolated rabbit heart and under conditions of reduced ventricular filling the rabbit and in the intact dog heart. From these data they concluded th the greater contractile force found in hypothermia is not due to release epinephrine or greater diastolic stretch, but to a direct effect of cold on t myocardium.

In summary, the observation of an increase in ventricular contractile fo in hypothermia supports the conclusion, reached by pulse contour analy and measurements of cardiac work performance and efficiency, that my cardial function is not impaired at low temperatures.

The Effect of Hypothermia on the Coronary Circulation

In these experiments, open-chest dogs anesthetized with pentobarbi (30 mg./kg.) were subjected to immersion hypothermia. Care was taken prevent ice water from entering the chest cavity. Blood from a caro artery supplied the cannulated left circumflex coronary artery. A pum reservoir system that permitted adjustment of perfusion pressure and a ro meter[13] for mean blood flow measurement were placed in the circuit (FIGU 4). In experiments in which phasic coronary blood flow was measured t rotameter was replaced by a bristle flow meter.[19] The immediate effe of dermal contact[20] with ice water are depicted in FIGURE 5. Within 1 2 min. after immersion in ice water, coronary blood flow was observed increase and continued to rise during the next 4 to 8 min. Experimen adjustment of perfusion pressure to the preimmersion level (points at and 8.5 min.) failed to return coronary blood flow to control values. T decrease in coronary resistance is assumed to be related to the increas

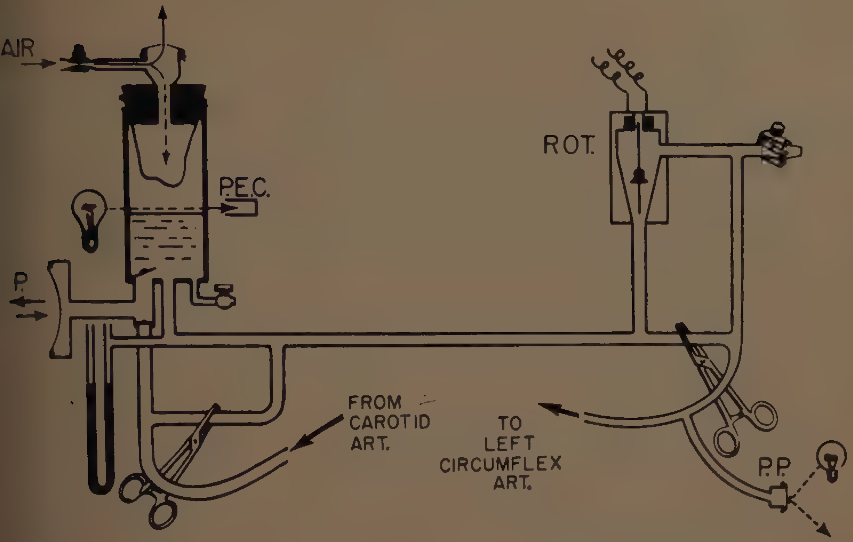

FIGURE 4. Schematic diagram of the apparatus used in perfusion of the left coronary rtery or its circumflex branch in the open-chest dog. Key: P, pump; P.E.C., photo-lectric cell; Rot, rotameter; P.P., perfusion pressure.

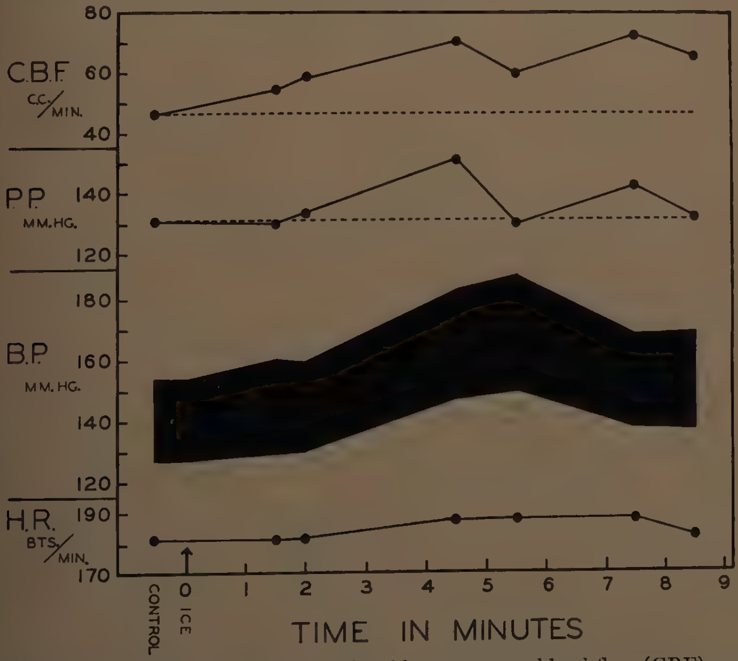

FIGURE 5. Effect of dermal contact with cold on coronary blood flow (CBF), perfusion ressure (P.P.), systolic and diastolic blood pressure (B.P.), and heart rate (H.R.). At .5 and 8.5 min. perfusion pressure was restored to control level. Reproduced by permis-ion from *Proceedings of the Society for Experimental Biology and Medicine.*[20]

cardiac work (increased blood pressure) associated with initial contact wi severe cold.

In progressive generalized hypothermia the reduction in body temperatu was associated with a decrease in coronary blood flow.[9, 21, 22] FIGURE 6 a plot of coronary blood flow against perfusion pressure for a single expe ment during the development of hypothermia. In moderate hypotherm (from 40° to 28° C.) coronary blood flow fell sharply at a time when perfusi pressure was relatively well maintained. At the lowest temperatures (21° 20° C.), however, coronary blood flow appeared to be stabilized in the pr ence of a falling perfusion pressure (aortic pressure). Elevation of perfusi pressure at a temperature of 21° produced curve B. Significantly high coronary blood flows were obtained in curve B than in curve A at equal pr sures, indicating a reduction in coronary resistance at 21° C. If, howev coronary resistance is calculated by dividing pressure by flow at vario points along curve A, one obtains a sharp increase in resistance in moder hypothermia and a return to approximately control values at the very l temperatures. Although changes in blood viscosity and in magnitude a duration of extravascular compression affect the pressure-flow relations in hypothermia, the two principal factors probably are the metabolic activi of the heart and the direct effect of cold on the coronary vessels. For t normothermic heart the pressure-flow relationship is depicted in FIGURE The point where the two lines cross in FIGURE 7 represents the mean aor pressure and the coronary blood flow that existed in this particular experime

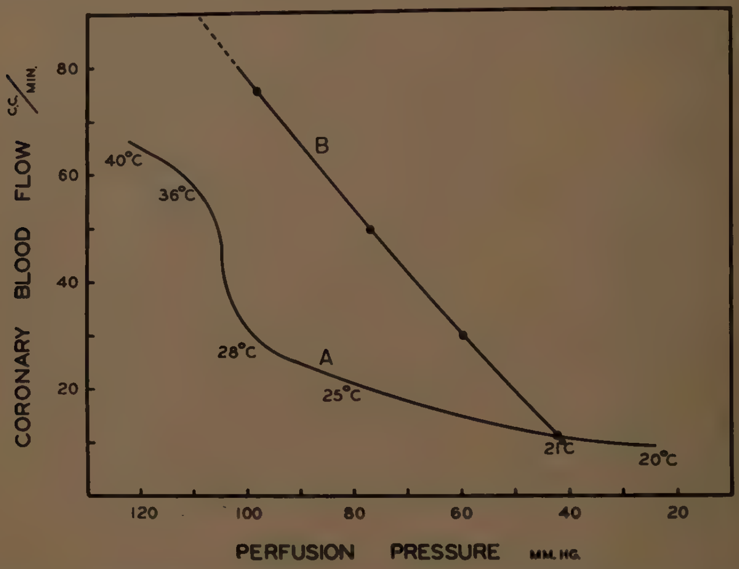

FIGURE 6. Pressure-flow relationship in progressive hypothermia, curve A. Effect t elevation of perfusion pressure on coronary blood flow at temperature of 21° C., curve Reproduced by permission from *Circulation Research*.[21]

t the time the surgical preparation was complete. From this point pressure as suddenly elevated or reduced to various levels. The flows observed nmediately after change in pressure are represented by the closed circles. lowever, flows progressively changed toward the control levels following ny given alteration in pressure and flows observed once stabilization occurred ibout 30 sec.) are represented by the open circles. Throughout this experi- ient aortic pressure and heart rate remained unchanged. The oxygen equirement of the myocardium probably changes very little during such an

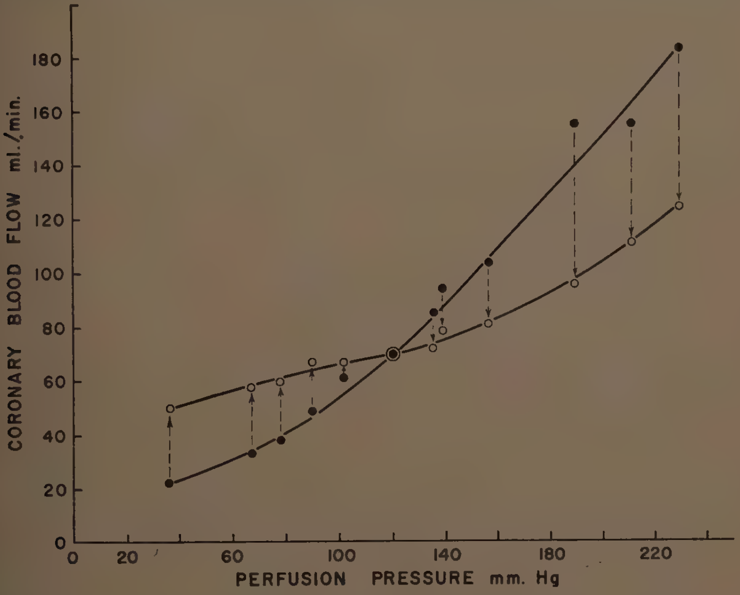

FIGURE 7. Pressure-flow relationship in the normothermic heart. Closed circles repre- ent flows obtained immediately upon increasing or decreasing perfusion pressure from the oint where the curves cross (control pressure and flow). Open circles represent flows bserved after a steady-state flow was reached following abrupt changes in perfusion ressure.

xperiment, and the alterations in flow represent intrinsic adjustments of oronary resistance which tend to maintain a constant supply of oxygen to he myocardium. In FIGURE 8 are replotted the pressure-flow relationship 1 hypothermia from FIGURE 6 and the lower segment of the steady-state ormothermic pressure flow curve from FIGURE 7. It is obvious that at qual pressures the flow was considerably greater in normothermia than in ypothermia, indicating a much higher resistance in the hypothermic heart. lowever, the effect of severe cold on the coronary vessels was unmasked pon increasing perfusion pressure at a blood temperature of 21° C. An ntirely different pressure-flow curve was described and resistance decreased rogressively as pressure was increased. At 90 mm. of mercury pressure esistance of the hypothermic heart became less than that of the normother- nic heart.

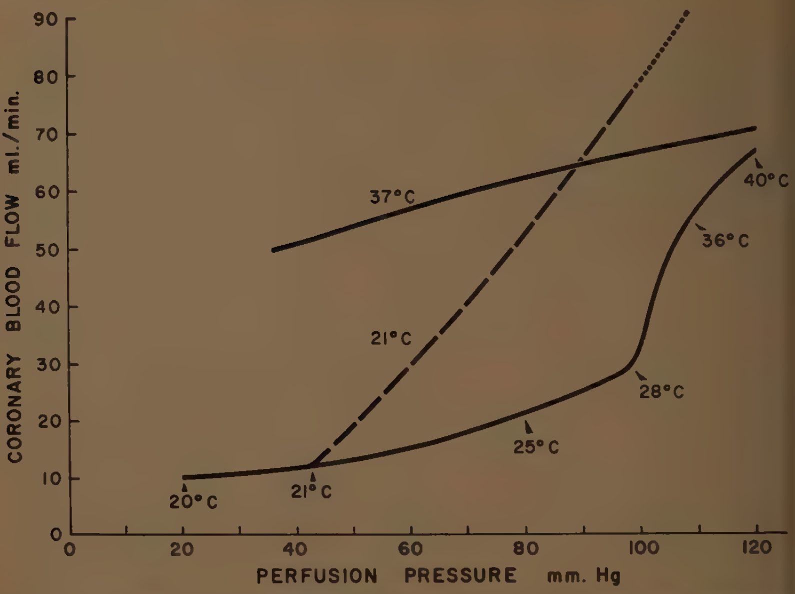

FIGURE 8. Comparison of pressure-flow curves in normothermia and hypothermi Dashed line represents coronary blood flow obtained upon elevation of perfusion pressu in hypothermia.

In normothermia at a constant cardiac work load and in the presence of low perfusion pressure, products of metabolism possessing vasodilator acti ity probably accumulate and bring about a decrease in coronary resistan At normal perfusion pressure myocardial oxygenation is likely to be adequa for myocardial needs, and vasodilator substances probably are present much lower concentration and perhaps may even be washed out of the hea

TABLE 3
EFFECT OF THORACIC AORTA CONSTRICTION ON CORONARY BLOOD FLOW IN HYPOTHERMIA

Temperature °C.	Heart rate beats/min.	Aortic pressure mm./Hg	Coronary blood flow ml./min.
36	120	138/104	46
23	43	48/26	26
23	46	80/42	44
37	150	156/110	110
28	96	96/70	87
28	96	122/86	107
35	143	134/110	52
21	22	64/32	23
21	21	136/61	72

t high pressures, resulting in an increase in coronary resistance. In hypoiermia, on the other hand, the work load of the heart is small and, since iyocardial oxygenation probably is adequate,[21, 23] it would appear that ccumulation of vasodilator metabolites would be improbable. Therefore can be reasoned that, in hypothermia, changes in myocardial metabolite oncentration as a function of coronary flow would be negligible. In short, ie vasodilating effect of cold would not be opposed to a significantly greater xtent at high than at low perfusion pressures. Similar reductions in resistnce were found with phasic coronary blood flow measurements (TABLE 3).

TABLE 4

EFFECT OF COOLING BLOOD PERFUSING THE CANNULATED CORONARY ARTERY ON CORONARY RESISTANCE

emperature °C.	Coronary blood flow ml./min./100 gm. heart	Perfusion pressure mm. Hg	Aortic pressure mm. Hg	Heart rate beats/min.	O₂ Consumption ml./min./100 gm. heart
36	72	119	148/123	200	
23	81	119	147/126	200	
37	73	96	122/96	200	
23	94	95	114/90	200	
39	61	119	118/98	180	
23	107	111	116/93	180	
39	78	108	125/102	200	
25	142	108	124/98	180	
38	81	110	132/102	180	
39	49	102	112/80	160	
31	68	105	113/84	160	
39	59	100	116/94	160	
38	45	118	97/78	120	
24	92	118	90/60	140	
42	45	119	88/60	120	
21	95	116	82/56	120	
37	68	99	128/85	140	6.3
25	82	100	108/72	140	7.3
35	67	100	117/85	135	5.0
25	83	99	113/82	140	6.6
37	54	99	121/93	120	6.4
23	86	99	118/90	120	6.6
38	74	99	127/97	140	6.1
22	102	98	127/99	120	6.8
37	82	99	75/44	140	5.7
24	141	99	66/36	140	9.4
37	103	100	87/62	140	7.2
24	142	95	67/40	140	8.5

At low temperatures when only partial restoration of aortic pressure wa produced by constriction of the thoracic aorta, coronary blood flow returne to control levels in the first two experiments and exceeded control levels the third. Since a reduction in blood temperature from 37° to 20° C. induc a twofold increase in viscosity of blood,[2] the observation of a decrease coronary resistance in hypothermia indicates an appreciable alteration in th caliber of the coronary vessels.

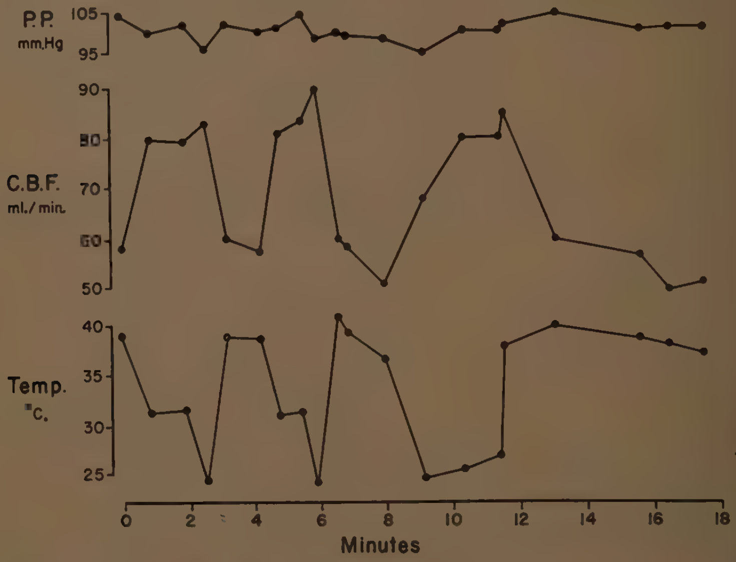

FIGURE 9. Effect of changing the temperature of blood perfusing the left circumfl coronary artery on flow through this vessel in the fibrillating dog heart.

Metabolic requirements of the heart are altered during immersion hyp thermia and thereby influence coronary blood flow. To eliminate this va able and to determine the effect of temperature per se on the coronary vesse experiments were performed at relatively constant levels of myocard oxygen consumption. In these experiments, the left coronary artery or circumflex branch was perfused from the carotid artery and a coil was plac in the external circuit for the purpose of cooling the blood perfusing the ca nulated vessel. Upon cooling, the blood entering the left coronary arte produced an increase in coronary blood flow with little or no change heart rate or blood pressure (TABLE 4). In three experiments oxygen co sumption of the left ventricle was measured and was found to increase sligh at the higher flows. In the fibrillating dog heart with the left circumfl coronary artery perfused by a donor dog a similar inverse relationship betwe the coronary blood flow and the temperature of the perfusing blood obtain (FIGURE 9). Anrep and Häusler[24] made similar observations in the dog hea lung preparation, and Cruickshank and SubbaRau[25] demonstrated a relaxi effect of cold on isolated rings of coronary vessels. Recently Covino a eavers[26] have reported this type of direct vasodilator effect of cold on the essels of skeletal muscle.

The extent to which heart rate per se affects coronary blood flow in hypo-ermia can be appreciated best by increasing the rate of the hypothermic eart toward control levels by left atrial stimulation. The results of such an periment are presented in FIGURE 10. The solid line represents the ter-inal segment of a pressure-flow curve obtained during the development of

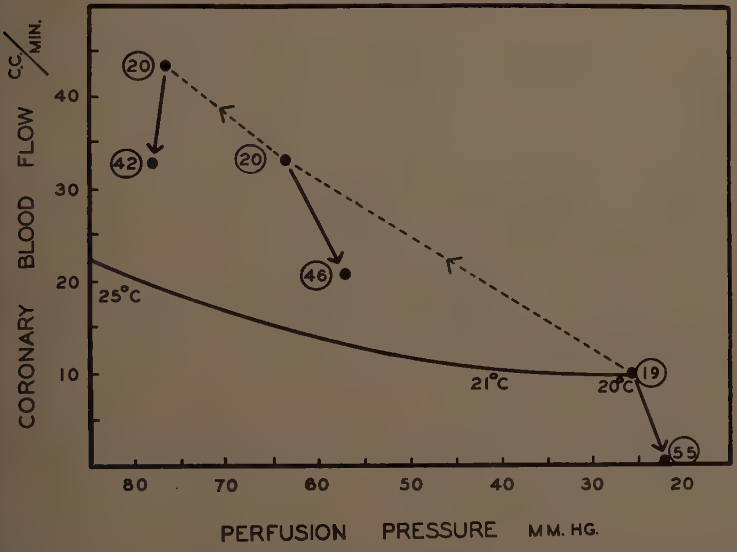

FIGURE 10. Effect of cardiac acceleration on coronary blood flow in hypothermia. lid line represents the terminal segment of a pressure-flow curve in hypothermia. En-cled numbers indicate heart rate and the points beside the numbers designate the pres-re and flow at each heart rate. The dashed line represents the flow obtained upon vation of perfusion pressure at a temperature of 20° C. Reproduced by permission m *Circulation Research.*[21]

pothermia. At 20° C. an increase in heart rate from 19 to 55 beats/min. duced coronary blood flow to zero. At higher flows, induced by raising rfusion pressure (dotted line), similar increases in rate resulted in a decrease flow. The reason for this reduction in flow with increasing heart rates in pothermia can be gleaned from FIGURE 2. In record A of FIGURE 2, at a te of 16 beats/min. the prolonged period of isometric relaxation was com-ete before the next systole occurred, whereas in record D, at a heart rate of beats/min. atrial systole occurred before the atrioventricular valves ened, and ventricular systole took place before there had been adequate ne for ventricular relaxation and filling. Consequently, there are two ects that may restrict coronary flow: first, the prolonged state of extra-scular compression existing throughout most of the cardiac cycle and, cond, an impaired ventricular filling and output resulting in a fall in aortic essure. If, however, heart rate is increased by the use of epinephrine, a different situation prevails. In TABLE 5 are the results of two such expe ments. In each instance perfusion pressure (mean aortic pressure), hea rate, and coronary blood flow were increased upon intravenous administrati of epinephrine. Associated with these changes were a reduction in the dur tion of systole and a reduction in the period of ventricular relaxation. Cons quently, extravascular compression was terminated before the onset of th next beat and did not impair significantly coronary inflow or ventricul filling. Despite the hemodynamic improvement with epinephrine, ventric lar fibrillation supervened within a matter of minutes. It is believed th the onset of ventricular fibrillation is a result of the stimulatory effects epinephrine on oxidative metabolism of the myocardium, under conditio of inadequate oxygen supply.

TABLE 5

EFFECT OF INTRAVENOUS EPINEPHRINE ON THE CORONARY CIRCULATION IN HYPOTHERMIA

Epi. mg.	Perfusion pressure mm. Hg	Heart rate beats/min.	Coronary blood flow ml./min.	Duration of Systole sec.	Duration of Ventricular relaxation sec.	Temperatur °C.
0	27	8	12	1.16	0.80	20
0.04	46	21	22	0.52	0.46	20
0	28	10	6	1.30	0.82	19
0.10	101	41	50	0.67	0.39	19

The role of extravascular compression in determining coronary blood fl in hypothermia may be evaluated by simultaneous recording of phasic co nary blood flow and pressure pulse contours. Results of such an experime are presented in FIGURE 11. Phasic coronary flow curves in normotherm (top record) and hypothermia show a rise with the onset of diastole. normothermia, peak flow was reached early in diastole, and from this poi until the onset of the next systole, phasic flow followed the decrease in aor pressure. Phasic coronary flow in hypothermia is characterized by a ma peak in systole and a minor peak very late in diastole. In hypothermia t flow during diastole increased in the face of a declining aortic pressure a continued to increase for 0.6 sec. after ventricular filling started. Associat with this rising diastolic coronary flow of hypothermia was a continu decline in ventricular pressure. At normal body temperatures, howev ventricular pressure rises during diastole as the ventricles fill; this ris ventricular pressure is associated in time with a decrease in coronary blo flow. Even if the heart rate is slowed at 37° C. by right peripheral vag nerve stimulation (record B, FIGURE 12) coronary blood flow was still fou to decrease throughout the major part of diastole. To make comparison flow and pressure curves at normal and reduced temperatures more read pparent, a slow camera speed was used in hypothermia (records C and D, IGURE 12). Elevation of aortic and ventricular pressures by aortic contriction in hypothermia (record D, FIGURE 12) increased the magnitude, but lid not effect the directional changes of coronary flow curves and pulse ontours (record C). The third beat in record D occurred prior to opening

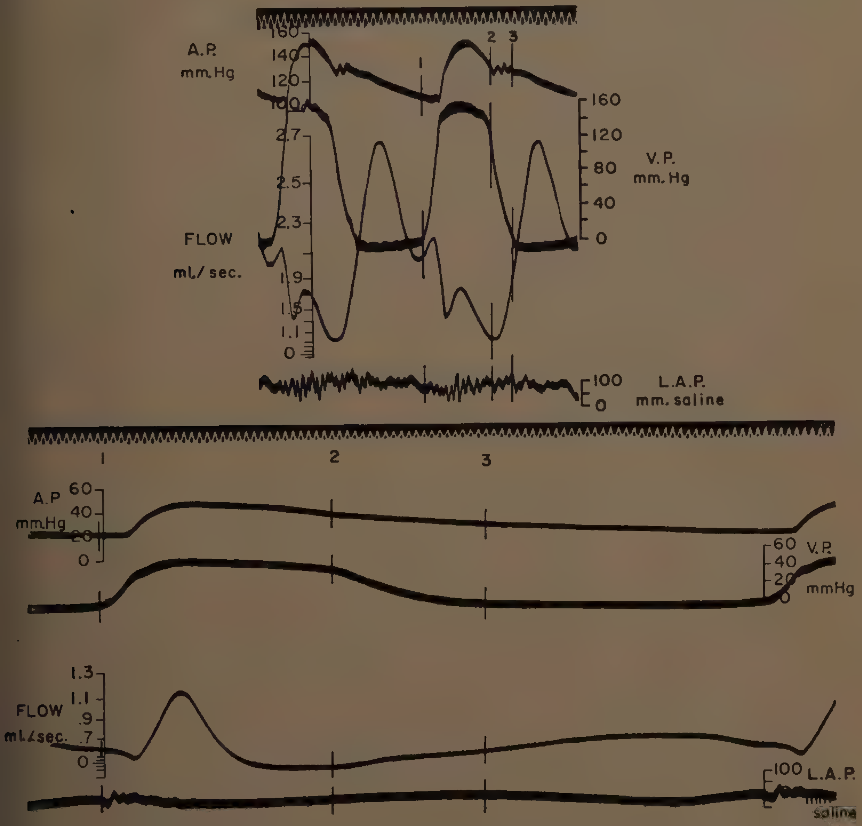

FIGURE 11. Phasic coronary blood flow in normothermia (*top*) and hypothermia. Key: A.P., aortic pressure; V.P., left ventricular pressure; L.A.P., left atrial pressure; , onset of systole; 2, end of systole; 3, opening of mitral valve. Time scale 0.02 sec.

f the mitral valve. Consequently, little blood was ejected into the aorta nd the compressing effect of the ventricular muscle was practically unopposed. Relaxation of the ventricles following this beat was also associated with a rise in coronary blood flow and a decrease in ventricular pressure. However, late in diastole coronary flow started to decline at the same time hat ventricular pressure began to increase.

These findings indicate that ventricular relaxation is greatly prolonged in hypothermia, extending well beyond the point of opening of the atrioventricular valves. Since the ventricular pressure in diastole is the algebrai sum of the fall in pressure due to ventricular relaxation, and the rise due t ventricular filling, the observation that ventricular pressure decreases fo the major part of diastole in hypothermia signifies that ventricular relaxatio is the predominant factor in determining diastolic ventricular pressure. Th slow ventricular relaxation of hypothermia is also the principal factor respon sible for the pattern of coronary flow in diastole.

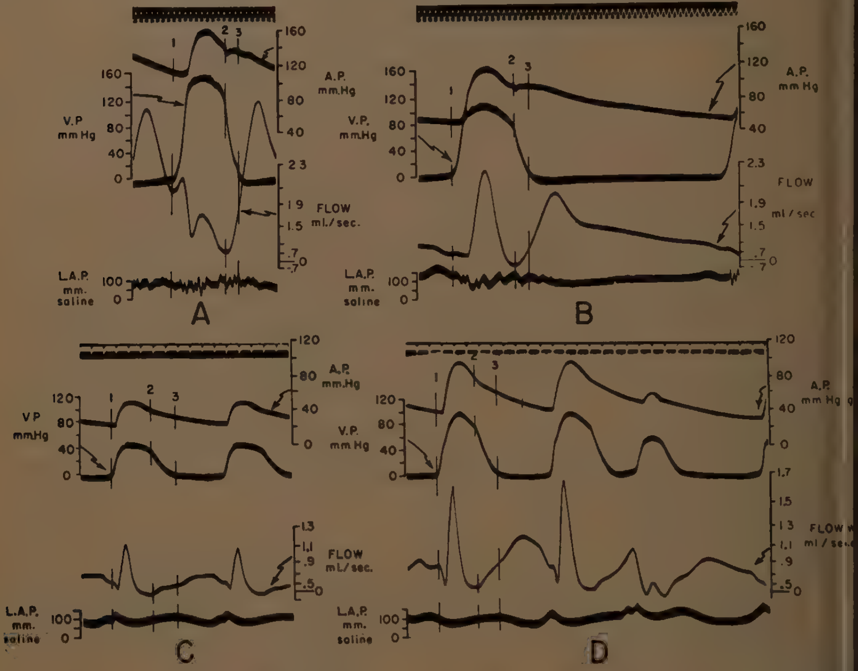

Figure 12. Phasic coronary blood flow in normothermia (A), normothermia wit peripheral right vagus nerve stimulation (B), hypothermia (C), and hypothermia wit aortic constriction (D). Key: A.P., aortic pressure; V.P., left ventricular pressure; L.A.P left atrial pressure; 1, onset of systole; 2, end of systole; 3, opening of mitral valve. Tim scale records A and B, 0.02 sec.; records C and D, 0.20 sec.

Summary

(1) As judged by three methods, namely, pressure pulse contour analysi cardiac work performance and efficiency measurements, and direct measur ments of myocardial contractile force, myocardial function in hypothe mia appears to be adequate for the work required of the heart at reduce temperatures.

(2) Cold induces a decrease in coronary resistance in severe hypotherm by a direct effect on the coronary vessels or possibly by retarding the rate destruction of a vasodilator substance.

(3) Myocardial function and coronary blood flow are adversely affected artificially induced increases in heart rate in hypothermia.

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RESPIRATION AND HYPOTHERMIA

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Introduction

Hypothermia alters virtually every measurable phenomenon in the field respiratory gas transfer. The blood-gas relationships are altered by th increased solubility, elevated pH, elevated pK, shifted dissociation curve oxygen, and the concern about bubble formation on warming. The contr of respiration is depressed both centrally and reflexly. The lung is altere by an increased dead space, and varying degrees of metabolic acidosis ha been reported. Since these phenomena have been extensively studied an reported, the present paper is a review and condensation of previous wor

Blood Gases During Hypothermia: The Physicochemical Laws

The alterations in solubility and blood pH resulting from even a few degree of temperature change are sufficient to invalidate the usual methods of dete mining gas tensions, calculating alveolar ventilation, alveolar O_2 tension, an physiological dead space at 37° C. For example, blood drawn at a bod temperature of 25° C. and analyzed in the same manner that would be use at normal body temperature will appear to have O_2 and CO_2 tensions 50 t 100 per cent too high. Certain errors have arisen from failure to make th appropriate temperature corrections or to change the methods.

The Oxygen Dissociation Curve

A nomogram, FIGURE 1, has been prepared for calculation of the effect temperature and pH on the dissociation curve.[1]

Changes in temperature and pH alter the position but not the shape of th oxygen dissociation curve. Dissociation curves for various values of pH an temperature for man may be computed from the 1 standard curve for norm human blood at 37° C., pH 7.4, by multiplying all the P_{O_2} values by facto for temperature and pH. The left-hand line gives factors for temperatur the next line factors for pH. The 2 right-hand line graphs give the standar oxygen dissociation curve in a form more easily read than the usual grap The computation is given by:

$$P_{t,pH} = P \times f_t \times f_{pH}$$

where $P_{t,pH}$ is the p_{O_2} at temperature t and pH, P is the P_{O_2} at 37° C, pH 7 for the same percentage of saturation, given on the standard curve, an f_t and f_{pH} are the multipliers obtained from the line charts.

The standard dissociation curve and the pH and temperature factors a taken from curves drawn by Dill and Forbes.[2, 3] Tensions at the high en of the curves were taken from Nahas *et al.*[4] These are believed to be averag curves, subject to some variation in normals and perhaps great variation

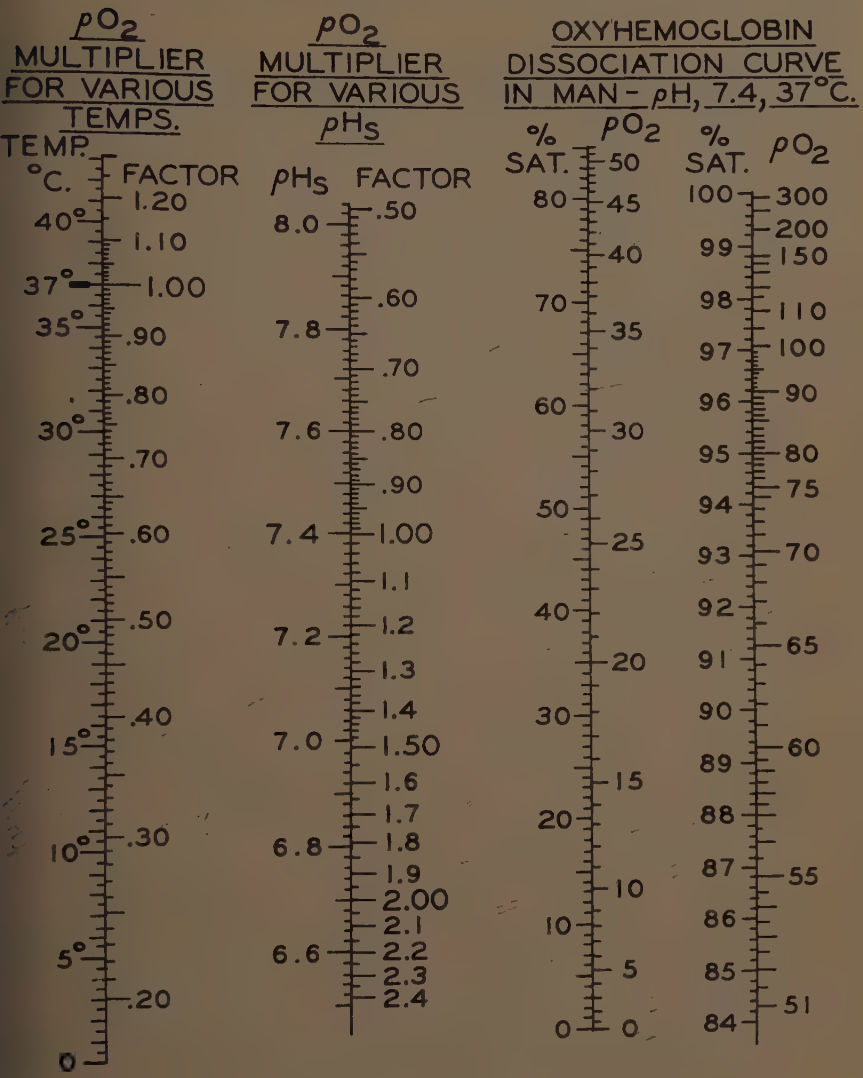

Figure 1

disease, particularly diabetes and anemia. The chief reason for variation is failure of intracellular *p*H, which more closely determines the affinity of hemoglobin for oxygen, to be constantly related to serum *p*H.

The shift of the O_2 dissociation curve with reduction of temperature has the effect of making less O_2 available to the tissues at a given tension in the blood and of making the hemoglobin more completely saturated in the lung at a given tension. There is also a small increase in dissolved O_2 amounting to 50 per cent at 20° C. Since the tissue need for O_2 is reduced, the dissolved

O_2 may supply a large portion of the metabolic needs, particularly if highl inspired O_2 concentrations are provided. This effect is somewhat reduce by the concurrent reduction in cardiac output, which will deliver less volume of O_2 to the tissues per minute.

Determination of pK

It has been assumed since 1928 that *p*K is 6.105 at 38° C. and 6.19 at 20° C. varying in linear fashion between these temperatures. These data are base

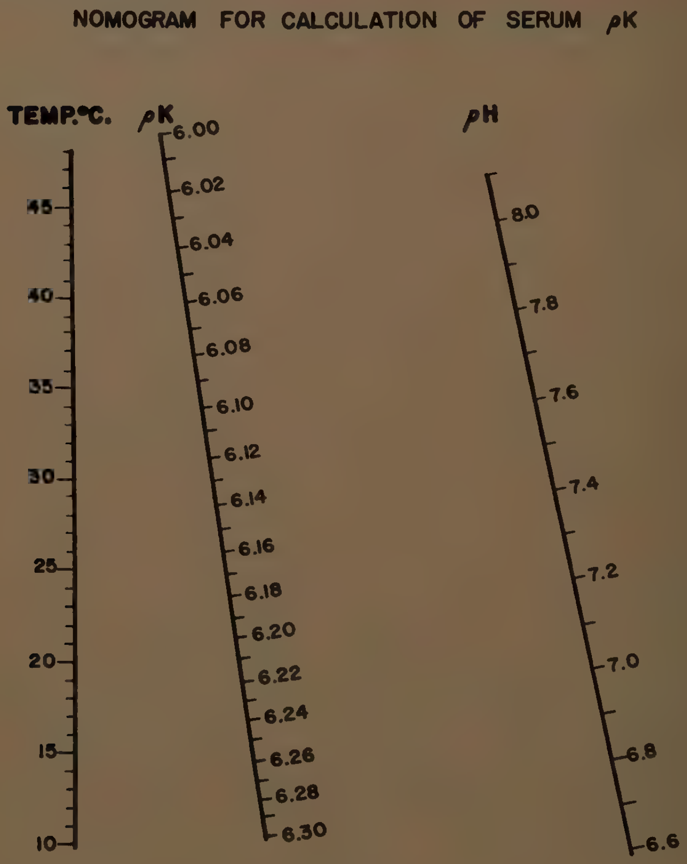

FIGURE 2

on an averaging of several investigators' data compiled by Hastings *et al.* and the determination of temperature sensitivity by Cullen *et al.*[6] To m knowledge, subsequent reports at variance with these have not been incorporated into investigative procedure. Robinson *et al.*[7] reported a larg number of *p*K determinations on human sera in 1934, averaging 6.09 Furthermore, if data on horse sera are omitted from Hastings *et al.*, th average is 6.094. With regard to temperature variations in *p*K, Rossier an

Mean[8] in 1941 reported variations twice as great as those observed by Cullen *et al.* Dill *et al.*[9] noted changes in *p*K with the *p*H of the serum in which the determination was made, corresponding to a rise of 0.03 for a fall in *p*H of one unit. With these conflicting data at hand, it seemed wise to determine the *p*K variations with temperature and *p*H, as they would affect our observations. A further reason was that *p*H standards have been changed through the years, and that previously most of the data were obtained with hydrogen electrodes, whereas most investigative work now is done with the glass electrode.

My 41 determinations on 9 sera agree well with those of Robinson, suggesting that *p*K is 6.090 at 37.5° C., *p*H 7.4. I found the increase of *p*K with falling *p*H to be slightly greater than did Dill *et al.*, my slope being 0.042. At 24° C. this slope was increased to 0.062, and the rise of *p*K at *p*H 7.4 agreed with Cullen, a value of −0.005 per degree being found. These data[10] have been incorporated into a nomogram (FIGURE 2) for the calculation of human serum *p*K at various temperatures and *p*H values.

Effect of Temperature on pH

The data of Rosenthal[11] indicate a linear rise in *p*H of blood and plasma cooled *in vitro*. The factor, −0.0147 units/°C. for blood and −0.0118 units/°C. for plasma, is said by some investigators to change with *p*H and perhaps with electrolyte, hemoglobin, and other concentrations, but no definitive study is available concerning this.

Effect of Temperature on CO_2

Rosenhain and Penrod[12] reviewed this material. One consideration often neglected in the search for extreme accuracy is the existence of 2 separate standards of solubility for CO_2. The earlier ones, based on Van Slyke and Sendroy's data, give a factor of 0.0301 mM/liter serum/mm. Hg P_{CO_2}. In a subsequent evaluation, Dill and Forbes[2] suggest that the blood used in Van Slykes' data had a lower-than-normal water content, hence a low CO_2 solubility. They suggested that the normal figure should be 0.0306 at 38° C. All of my previous data on *p*K and *p*H and P_{CO_2} were based on the lower and probably incorrect figure. Fortunately, however, the *p*K and the solubility must be made to fit each other by tonometric analysis of blood, measuring *p*H, P_{CO_2}, and CO_2 content. The *p*K I used, shown in the nomogram, is based on 0.0301. If 0.0306 is used a *p*K higher by 0.009 units, or 6.10 at 37.5° C., *p*H 7.4 should be employed.

The effect of temperature on P_{CO_2} and P_{O_2} of blood *in vitro* was reported by Bradley.[13] Nomograms were presented allowing correction for differences between temperature of measurement and body temperature. The changes are roughly 4 per cent/°C. for P_{CO_2} and 6 per cent/°C. for P_{O_2}. These data have not been adequately confirmed experimentally, since studies in my laboratory are still under way.

This changing gas tension must be kept in mind because of the problem of bubble formation in the use of warming coils or in cold blood pumped into warm patients. In either case, if the total gas tension in the blood is atmospheric before warming, warming will result in bubble formation and ga embolism.

The nomograms used for interrelating *p*H, P_{CO_2}, and CO_2 content o buffer base are valid only at 37.5° C., and will introduce very large errors i used on blood from hypothermic patients.

Physiology of Pulmonary Function During Hypothermia

Hypothermia depresses the spontaneous respiratory exchange. The mag nitude of this depression and the temperature of its endpoint, apnea depend greatly on the depth of anesthesia, the type and amount of premedication, and individual variations, thus precluding any valid prediction of thes quantitative ventilatory responses to hypothermia. Usually it is assume that assistance to or control of respiration is desirable during hypothermia

Whenever artificial respiration is used, questions arise concerning it effect on the blood gas tensions, the *p*H, and the circulation. At 37° C the problem is the maintenance of normal values. At reduced temperature an additional problem presents itself: What are the most desirable value of *p*H and P_{CO_2}, there being no normal? If one holds *p*H or P_{CO_2} constant CO_2 is retained. In other species *p*H may rise during cooling, as in alligator or fall as in hibernators. The current favoring of hyperventilation is base largely on the incidence of ventricular fibrillation in animals cooled withou assisted respiration. On the other hand, vigorous hyperventilation ma deprive tissue of oxygen by two factors: (1) the rising *p*H further shifts th oxygen dissociation curve to low tensions, and (2) cardiac filling and outpu are reduced.

A further complication arises when an attempt is made to relate ventilation as measured by tidal volume and respiratory rate, to the resultant *p*H an P_{CO_2}. At 37° C. these relationships are conveniently obtained from diagrams During hypothermia, the metabolic production of CO_2 falls, solubilitie change, and the lung may behave differently. Reports have suggested that during hypothermia, CO_2 elimination from the lung somehow may b blocked.[14] We have, therefore, performed the following experiments t establish some of the relationships between ventilation and blood gases durin hypothermia.

Dogs were curarized, anesthetized, ventilated at known rates with know volumes of air, and cooled in ice packs. Determinations included lung compliance, arterial blood *p*H and P_{CO_2}, end-expiratory P_{CO_2}, expired air CO_2 concentrations, anatomic and physiological dead space, and alveolar ventilatio Results are as follows (TABLE 1):

(1) The anatomic or airway dead space at 25° C. was increased by 50 pe cent. A similar increase in the warm animal is obtained with atropin Bronchoconstriction resulting from vagal stimulation, easily observed as decreasing anatomic dead space, is blocked at 25° C. The cardiodepresso effect of vagal stimulation is greatly depressed or absent at 25° C.

(2) Physiological dead space, calculated from the Bohr formula usin arterial P_{CO_2}, is also increased during hypothermia, again due to bronchodilatation.

(3) Alveolar dead space, a portion of the physiological dead space due to uneven distribution within the lung, is unchanged during hypothermia. If there were any block in CO_2 excretion, from any cause, it would be expected to enlarge this value.

(4) The difference between arterial and alveolar (end-expiratory) CO_2 tensions is a further measure of uneven distribution, primarily of blood flow.

TABLE 1

EFFECTS OF HYPOTHERMIA ON PULMONARY FUNCTION IN ARTIFICIALLY VENTILATED DOGS

	No. of dogs	Warm	Cold	Change
Temperature °C	27	37.4 ± 1.3	24.7 ± 1.3	−12.7°
Respir. rate/min	27	14 ± 4	14 ± 4	
Tidal vol., ml. BTPS	27	203 ± 70	194 ± 61	
Compliance, ml./cm. H_2O	19	20.9 ± 5.7	16.8 ± 4.0	−19%
$\dot{V}_{CO_2}$, ml./min. STPD	24	65 ± 20	28 ± 9	−57%
$\dot{V}_{O_2}$, ml./min. STPD	5	56 ± 11	18 ± 7	−68%
R, exchange ratio $\frac{\dot{V}_{CO_2}}{\dot{V}_{O_2}}$	5	1.00 ± .08	1.51 ± .28	+51%
*p*H	27	7.28 ± .12	7.37 ± .12	+0.09
CO_2 mM/l., plasma	27	19.7 ± 3.8	16.5 ± 3.7	−16%
CO_2 c.p.	27	19.8 mM/l.	16.0 mM/l.	−19%
P_{CO_2}, mm. Hg (art.)	27	39.5 ± 8.1	23.1 ± 5.9	−42%
P_{CO_2}, mm. Hg, end-tidal	27	35.2 ± 7.1	19.3 ± 5.9	−45%
a-A P_{CO_2} diff., mm. Hg	27	4.3 ± 6.5	3.8 ± 4.1	
Same, in % of Pa_{CO_2}		11%	16%	+5%
Dead spaces, ml., BTPS				
Anatomic	10	60 ± 18	90 ± 29	+50%
Physiol	19	76 ± 32	97 ± 41	+28%
Alveolar	9	15 ± 27	13 ± 31	
Alveolar, % of alv. V_T	9	10	12	+2%

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This difference was not altered or often reduced during hypothermia, again suggesting no impairment in CO_2 excretion.

(5) The slope of the alveolar nitrogen plateau after a single breath of oxygen is a measure of uneven ventilation. No significant change was observed in this slope.

(6) As temperature falls, provided tidal volume and rate are held constant, the arterial P_{CO_2} at 25° C. falls to about one half the control value. This fall reflects a comparable decrease in metabolism. The arterial *p*H usually rises 0.1 unit.

(7) Metabolic acidosis occurs to a variable extent, both at 37° C. and during cooling, depending on the occurrence of hypoxia and respiratory acidosis (TABLE 2).

(8) Compliance tends to decrease during hypothermia, but not significantly more than during a similar span of time at 37° C. This progressive fall is probably due to lung changes, such as atelectasis.

In summary, hypothermia leads to an increased anatomic dead space through bronchodilatation, but no evidence of difficulty in elimination of carbon dioxide has been observed, provided the known changes in blood gas tensions are considered.

TABLE 2

NORMAL MAN: EFFECT OF OXYGEN, ATROPINE AND DEEP BREATHING

No. of subjects	V_T	Pa_{CO_2}	Alveolar dead space		a-A P_{CO_2} difference	
			ml.	%	mm. Hg	%
Breathing air						
10	624	38	20	4 ± 6	0.9	3 ± 10
Breathing oxygen						
7	656	36	44	8 ± 2	3.6	11 ± 6
Breathing air, deeply, slowly						
6	2130	33	290	13 ± 5	1.4	4 ± 6
After atropine, 0.5 mg., s.c.						
5	594	38	25	5 ± 6	1.6	4 ± 4

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In man, control studies were done on 10 normal, awake, supine individual (TABLE 3). The mean alveolar dead space was 4 per cent of the alveolar tidal volume, or 20 ml. The mean arterial-alveolar (a-A)P_{CO_2} difference wa 3 per cent of the arterial P_{CO_2}, or 0.9 mm. Hg. This means that in the norma supine subjects less than 5 per cent of the alveoli are nonperfused. When seven subjects breathed oxygen for 5 min., the alveolar dead space rose to 8 per cent and the a-A P_{CO_2} difference to 11 per cent. The effect of deep slow breathing was to elevate the alveolar dead space (to 13 per cent), but not to change the a-A P_{CO_2} difference. Atropine had no effect on either index although it did enlarge the anatomic dead space.

Studies of the a-A P_{CO_2} difference with hypothermia were done on 5 patients with atrial septal defects, and 3 during neurosurgical procedures (TABLE 3) The day before surgery 4 of the subjects with atrial septal defects were found to have normal values (7 per cent), and the one measured neurosurgery patient showed a 4 per cent a-A P_{CO_2} difference. The induction of anesthesia, intubation, and control of respiration resulted in a rise to 15 per cent in the atrial septal defect cases, and a rise to 24 per cent in the other two neurosurgery patients (who were not studied awake). The actual cooling was accompanied by only slight increases in a-A P_{CO_2} difference, to 21 per cent in the cardiac cases, and to 26 per cent in the neurosurgical cases. The neurosurgical patients, when remeasured 2 to 4 hours later at about the same temperature (30° C.), had further increased in a-A P_{CO_2} to a mean of 33 per cent. It is probable that perfusion changes in the lung with time are progressive under anesthesia, both in the warm and cold state.

TABLE 3

AVERAGE EFFECT IN 5 PATIENTS OF HYPOTHERMIA AND CLOSURE OF ATRIAL SEPTAL DEFECT ON ARTERIAL-ALVEOLAR CO_2 DIFFERENCES AND CO_2 COMBINING POWER

Condition	No. subjects	Temp. °C.	*p*H	CO_2*	CO_2 c.p.	Art. P_{CO_2}	Alv. P_{CO_2}†	a-A P_{CO_2} difference	
								mm. Hg	%
Control, awake	4	37.2	7.43	25.5	25.4	36	33	2.1	7 ± 6
Endotracheal ether artificial resp.	5	35.9	7.46	22.7	24.4	29	25	4.4	15 ± 8
After ice water cooling	4	30.4	7.58	22.1	24.8	20	16	4.2	21 ± 8
Chest open, lung retracted	5	29.7	7.55	22.0	24.0	21	15	6.1	29 ± 8
Two to 10 min. postocclusion	5	29.3	7.42	19.7	20.2	27	12	15.	55 ± 9
Chest closed, before warming	4	29.4	7.49	19.9	21.5	21	11	10.	49 ± 13
End of rewarming	5	34.7	7.45	21.3	23.1	30	22	8.1	27 ± 10

* Plasma CO_2 content mM/l.

† End-tidal.

In the five cardiac patients, there occurred a further small rise to 29 per cent a-A P_{CO_2} difference on opening the chest and retracting the lung. The next sample was taken 2 to 10 min. after re-establishing the circulation following closure of the septal defect. The mean a-A P_{CO_2} difference had risen to 55 per cent of the arterial P_{CO_2} at this time. Even after closing the chest, a 49 per cent difference persisted and, at the end of rewarming in a warm bath, the figure had fallen to 27 per cent. There was surprisingly small scatter in the values during the immediate postocclusion period, which makes it possible to state that operative procedure and/or the period of cessation of circulation was followed by maldistribution of blood flow through the lung equivalent to nonperfusion of more than one half the pulmonary capillaries.

The estimated carbon dioxide-combining power in these patients (TABLE 3) did not fall during anesthesia or hypothermia, but did fall 4 mEq./l. after occlusion of the circulation, indicating that in man metabolic acidosis occurred from tissue ischemia, but not from hypothermia.

It seems apparent from these data that the actual process of cooling altered only slightly, or not at all, the distribution of blood flow through the lungs. Both the alveolar dead space and the a-A P_{CO_2} difference remained almost constant with decreasing temperature. Otis reported identical results while measuring a-A P_{CO_2} differences in hypothermic dogs.[15] There seems to be no evidence to suggest a pulmonary block of carbon dioxide excretion during hypothermia, since in both dogs and patients the P_{CO_2} fell with cooling, while tidal volume and rate were constant. Several other factors that contribute toward carbon dioxide retention during surgery and hypothermia follow.

Effect of Temperature on Blood-Gas Equilibria

By considering the increased solubility of carbon dioxide at low temperatures, the elevation of *p*H, and elevation of *p*K, it may be shown that, when blood is cooled anaerobically from 37° to 25° C., the P_{CO_2} will fall 42 per cent or from 40 mm. Hg to 22.9 mm. Hg. Thus, if blood carbon dioxide content remains constant, the alveolar tension in equilibrium with blood carbon dioxide falls, and less carbon dioxide is eliminated per minute by an unchanged ventilation. If carbon dioxide production were unaltered, carbon dioxide would gradually accumulate until P_{CO_2} rose to its precooling level. Actually, of course, metabolic carbon dioxide production is also reduced at low temperatures, tending to compensate for the fall in tension. In fact, in these experiments, as will be described, the two seemed to cancel out approximately, keeping blood carbon dioxide constant.

Metabolic Acidosis

The fixed acids appearing in blood during hypothermia in dogs and, after inflow occlusion, in man, may be thought of as having two effects requiring hyperventilation: (1) the fall in *p*H increases carbonic acid at the expense of body stores or bicarbonate, the P_{CO_2} is elevated and more carbon dioxide must be eliminated by the lungs; (2) usually the low *p*H is compensated for by increased ventilation.

Enlargement of Dead Space

It has been found previously[16] that hypothermia enlarges the anatomic dead space by bronchodilation similar to that seen after atropine. The small increases in physiological dead space demonstrated in these dogs are presumed to be due to the same mechanism, and they result in proportionate decreases in alveolar ventilation.

Maldistribution Due to Decreased Pulmonary Blood Flow

We may attempt to explain the very large a-A carbon dioxide difference found in patients after closure of an atrial septal defect and restoration of the circulation. These patients preoperatively were known to have left-to-right atrial shunting with very high pulmonary flow rates and, as judged by the data, they appeared to be perfusing their lungs uniformly. During inflow occlusion all the pulmonary capillaries have the opportunity to close. When circulation is restarted, it is with reduced pulmonary blood flow rates, and it seems reasonable to assume that not all the capillaries would reopen immediately. The pulmonary flow during this recovery phase is also reduced by the hypothermia itself and by myocardial depression following the period of anoxia. It does not seem difficult to believe that half the alveoli might have no blood flow under these conditions. In addition, air may be pumped from the open right heart into the pulmonary capillaries, producing emboli and obstructing blood flow.

Attempt to Define Normal Ventilation During Hypothermia

If we are to use terms such as hyper- and hypoventilation during hypothermia, we imply that we refer to some normal or euventilation at that temperature. What should be the definition of normal ventilation? Hypothermia is an abnormal state usually produced by anesthesia and drugs in varying amounts, so observation of cooled subjects is an unreliable source of this normal value. Either *p*H or P_{CO_2} might arbitrarily be held constant, but the observation of the rapid changes in both *p*H and P_{CO_2} when a sample of blood is cooled detracts from the rationality of using them. It is more reasonable to propose that normal ventilation is that in which carbon dioxide elimination equals its rate of metabolic production as cooling progresses. This definition has several characteristics: (1) blood carbon dioxide content remains unchanged; (2) *p*H rises *in vivo* at the same rate as in blood cooled *in vitro*, by 0.0147 U./°C.; (3) alveolar and arterial P_{CO_2} fall at the same rate as that of blood cooled *in vitro*, reaching 22.9 mm. at 25° C. However, if metabolic acidosis occurs, *p*H fails to rise so much, and extra carbon dioxide is eliminated. If ventilation is unchanged, P_{CO_2}, after a period of elevation due to the freed body stores, will return to the same level as in the absence of metabolic acidosis. Finally, then, it would appear that the P_{CO_2} should be used to define normal ventilation; not that P_{CO_2} should be constant, but that it should fall as the P_{CO_2} does in blood cooled *in vitro*. In the absence of metabolic acidosis, carbon dioxide elimination would keep pace with its metabolic production. Metabolic acidosis would result in a fall in carbon dioxide content and less than the expected rise in *p*H. Finally, with this normal ventilation, the carbon dioxide content at any temperature will equal the carbon dioxide-combining power (this is not intended to imply that this normal or euventilation level is empirically the best ventilation to ensure protection of the circulation in hypothermia; that must be settled experimentally).

What minute volume will provide this normal ventilation during hypothermia? By coincidence, in the dogs where ventilation was held constant in rate and depth during cooling, P_{CO_2} fell from 39.5 at 37.4° C. to 23.1 at 24.7° C., the predicted value being 22.9 at 25° C. The patients were mildly hyperventilated in both the warm and cold states by this standard, the predicted P_{CO_2} being 29 mm. at 30° C., whereas the observed mean P_{CO_2} was

20 mm. in the 4 cardiac patients and 27 mm. in 2 neurosurgical patients. Roughly, then, the changes in solubility and in the lung very nearly balance the decrease in metabolism. Normal P_{CO_2} as predicted for blood cooled *in vitro* therefore will be approximated by use of the same tidal volume and rate as were needed to maintain a P_{CO_2} of 40 mm. Hg at normal body temperatures.

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THE LIVER IN HYPOTHERMIA*

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In discussing the part played by the liver in the physiology of the hypothermic state in homeotherms, several aspects may be considered, including the role of the organ in the attempts of the organism to maintain or to restore normal body temperature; the new functional and biochemical equilibria established once the organ is at a subnormal temperature level; and, finally, the structural and functional changes in the liver of a homeotherm following exposure to hypothermia. In what follows each of these points of view will be adopted, in turn, in an attempt to give a rounded picture of the present knowledge of the subject. As it will become clear on perusal of this paper that such a discussion can be only in the nature of a progress report as of this date, we have taken occasion to point up gaps in current knowledge wherever possible.

Heat Production by the Liver in Relation to Temperature Defense

In normal mammals at rest the metabolic activity of the liver makes an important contribution to total heat production. About 50 per cent of the basal oxygen consumption of such animals takes place in the abdominal viscera,[1] and of this amount the liver would seem to account for at least one quarter. Calculations of liver oxygen consumption in several species of widely differing sizes suggest (TABLE 1) that this organ accounts for a fixed fraction, about 12 per cent, of the basal metabolic rate (BMR).[2] Since BMR is nearly proportional to body-surface area, the linear relation between BMR and liver oxygen consumption implies that the total liver metabolism also must vary with the body-surface area, rather than with body mass. This entails changes in Q_{O_2} of the tissue, as well as in the ratio of liver weight to body weight; as shown in TABLE 1, Q_{O_2} as well as liver/body weight ratios are high in small animals and lower in large ones. These relations appear to reflect the energy required to maintain the thermal equilibria that control body temperatures in these warm-blooded species.

Cold adaptation in the rat, as may be seen from TABLE 1, leads to increased metabolic rate, maintained even at normal ambient temperatures, and to increased relative liver weight and increased[3] liver Q_{O_2}. It might be said, therefore, that the cold-adapted rat tends to become an oversized mouse with respect to its liver metabolism (last column, TABLE 1).

Hepatomegaly has been observed in several groups of Eskimos inhabiting various sections of the Arctic.[4a] In contrast to the observations recorded above for the rat, in this case the condition appears to be due to nutritional factors and to be rapidly reversible. Hence hepatomegaly should not be viewed as a result of cold adaptation in these most efficiently clothed human subjects.

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* The work reported in this paper does not necessarily reflect the views of the Navy Department or the naval service at large.

The concept of the liver as an important thermogenic center in the resting homeotherm, first advanced by Dubois[4b] more than 70 years ago, derives its support not only from indirect considerations such as those presented above, but also from the observation that the temperature of the liver tends to exceed the temperature of the surrounding organs by 0.5° to 1.0° C. in resting euthermic mammals and birds. Indeed, liver temperatures under these conditions exceed those of all other organs except possibly the brain,[5] so that heat would be expected to flow from the liver to the rest organism. The magnitude of such heat flow must be determined largely by the rate of blood flow through the liver and by the temperature differential between the liver and other organs. In hypothermia, the liver temperature, in general, appears to follow closely the changes in deep colonic temperature, with minor variations apparently due to the specific cooling or rewarming techniques employed. This is true for the rat,[7] the dog,[6, 8] and for the hamster and the hibernating ground squirrel during the awakening sequence.[9a]

TABLE 1
LIVER OXYGEN CONSUMPTION IN RELATION TO TOTAL OXYGEN CONSUMPTION IN DIFFERENT SPECIES, AND THE EFFECT OF COLD ADAPTATION ON LIVER METABOLISM IN THE RAT*

Species	Body wt. (gm.)	Oxygen consumption (cc./hour)	Liver			
			Weight (percentages body wt.)	Q_{O_2} cc./hour/gm. wet wt.	Oxygen consumption as percentages of total	Oxygen consumption (cc./hour/gm. body wt.)
Mouse	20	33.8	6.2	3.3	12.4	0.21
Rat female (cold-adapted)	235	227	4.9	2.3	12.4	0.12
Rat female (weight control)	235	164	3.8	2.0	10.6	0.076
Dog	20,000	7,200	2.2	2.0	12.1	0.044
Man	70,000	14,700	2.5	~1.0	~11.8	0.025

* Data calculated from Fuhrman and Martin[2] and You and Sellers.[3]

The Q_{O_2} of liver tissue (in tissue slice experiments,[10] as well as in liver perfusion studies[11]) decreases with temperature at very nearly the same rate as the nonshivering whole body metabolism[6] (both being reduced by about 50 per cent for each 10° C. fall in temperature) so that the share of the liver in nonshivering heat production would be expected to be relatively independent of temperature. While no direct measurements of liver, or even of splanchnic, oxygen consumption have been reported either in established hypothermia or during the periods of active temperature defense, experience in other situations fails to indicate that the liver can respond to acute physiological stimuli with large increases of heat production. Thus, in moderately severe exercise the total oxygen consumption of man may increase from 50 Cal./hour/m.^{2} to 190 Cal./hour/m.^{2}; of this total metabolic rate, the abdominal viscera contribute an amount that decreases from about 50 per cent at rest to about 10 per cent during exercise, so that the total splanchnic oxygen consumption actually may decrease somewhat in the face of greatly increased production of muscular energy and heat.[1]

While the data on liver blood flow will be reviewed further on, it may be anticipated here that such results as are available indicate that in hypothermia the rate of blood flow through this organ is decreased to a degree that is certainly no less than the reduction in cardiac output and actually may exceed it. Taken together and added to the results of liver thermometry, these observations fail to support any special role of hepatic thermogenesis in the defense of body temperature during the induction or maintenance of hypothermia, or recovery from it, in the several homeotherms studied so far.

In line with this conclusion, it has been found that the course of spontaneous rewarming in the hamster awakening from hibernation is not altered in any way by evisceration,[9b] a most dramatic method of demonstrating that thermogenesis in the splanchnic viscera does not play a significant role in the recovery of normal body temperatures.

These conclusions regarding heat production in the liver, however, do not necessarily imply that the liver may not play some other role in connection with the metabolic responses associated with temperature defense. Thus, it has been noted that liver glycogen is depleted during the shivering stage of the induction of hypothermia in several species. Depletion of liver glycogen also is prominent during the awakening response of the hibernating hamster.[9a] Exclusion of the liver from the circulation, as by evisceration, allows these animals to regain near-normal body temperature, only to die promptly with severe hypoglycemia.[9b] In a slightly different vein it should be recalled, perhaps, that the specific dynamic action of fed protein in the hypothermic rat is proportionately, although not absolutely, far larger than in the normothermic animal,[12] a result largely attributable to changes in liver metabolism under the influence of this diet. Thus, it seems certain that the liver can respond to appropriate stimuli even in fairly deep hypothermia and that, therefore, it may well contribute to the defense of body temperature during hypothermia by regulating blood composition in important ways.

Liver Circulation in Hypothermia

Turning now to the functioning of the liver during the hypothermic state, it should be recalled at the outset that, as a chemical organ, the liver functions by effecting transfers of a wide variety of materials out of or into the blood passing through the hepatic vascular tree. Thus, liver function cannot be discussed here without a knowledge of hepatic circulation in hypothermia.

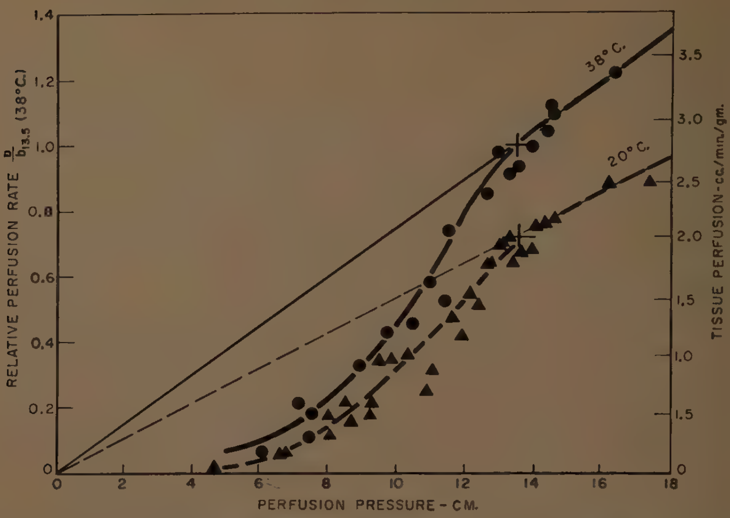

FIGURE 1. Flow pressure diagram for the isolated rat liver perfused with whole ra blood at 38° C. and at 20° C. Perfusion pressure, in cm. of blood; perfusion rates ar normalized for each preparation so that the value at 38° C. and 13.5 cm. perfusion pressur is 1.0. Reproduced by permission from the *American Journal of Physiology.*[13]

In vitro, the effect of hypothermia upon hepatic hemodynamics has bee studied in some detail.[13] The conclusion was reached that the changes i the flow pressure diagram of the isolated rat liver (FIGURE 1) are due largel to changes in blood viscosity; blood flow distribution or the distribution o critical closing pressures are changed little, if at all, by changes in perfusio

TABLE 2

CHANGES IN PERFUSION RESISTANCE OF THE ISOLATED, PLASMA-PERFUSED RAT LIVER AT VARIOUS TEMPERATURES*

Perfusion temperature (°C.)	$\frac{b}{b_{38° C.}}$	$\frac{\eta_{38° C.}}{\eta}$	$\frac{s}{s_{38° C.}}$
38	1.0	1.0	1.0
30	0.93	0.86	0.92
20	0.72	0.61	0.84

b = perfusion rate in cc./gm./min. when perfusion pressure P_b, equals 13.5 cm. H_2 (actual P_b is between 13.5 and 15.0 cm., that is, in the Poiseuille region of the flo pressure diagram).

η = plasma viscosity, Ostwald viscometer

s = resistance of hepatic vascular bed, derived from

$$s = \frac{P_b}{b_\eta}$$

* Calculated from data of Brauer *et al.*[13]

emperature[13] between 20° C. and 38° C. By using plasma as a perfusate in ieu of blood to eliminate the rheological complications associated with the low of whole blood through any vascular tree, it could be shown that cooling ctually results in a slight decrease of total hepatic resistance in this preparaion (TABLE 2).

TABLE 3

ESTIMATION OF THE EFFECT OF HYPOTHERMIA ON LIVER BLOOD FLOW *IN VITO*

A. Dog*

Colonic temperature (°C.)	Relative cardiac output**	Relative splanchnic blood flow ($ESBF_{BSP}$)	ϵ_{BSP}†
38°	1.00	1.00	0.27
30°	0.77	0.65	0.27
23°	—	0.37	0.27

B. Rat

Liver temperature (°C.)	Relative cardiac output‡	$CrPO_4$ Disappearance		
		$t_{1/2}$ (min)	$t_{1/2}^{38°}/t_{1/2}$	lim.ϵ§/$\epsilon_{38°}$C.
38	1.00	0.51 ± 0.11	1.00	1.00
30↓	0.73	0.86 ± 0.12	0.59	0.60
30↑	—	1.04 ± 0.17	0.50	—
20	0.33	2.10 ± 0.15	0.24	0.28

* From data of Hallett.[14]

** From data of Rosenhaim and Penrod.[15]

† Fraction of BSP removed from blood in a single passage through the liver.

‡ From data of Bullard.[20]

↓, cooling continued; ↑, during rewarming.

§ Fraction of $CrPO_4$ removed from blood in one passage through the liver; lim. $\epsilon/\epsilon_{38°}$ C. = the limiting ratio of ϵ as blood flow rate is increased.[19a]

Information on the hepatic circulation in intact hypothermic animals is, as yet, rather scanty. In the dog the Bromsulphalein (BSP) method has been used to estimate splanchnic blood flow as a function of rectal temperature in surface-cooled animals.[14] The results obtained are shown in TABLE 3A together with data on cardiac output in dogs cooled under apparently comparable conditions.[15] Since the proportion of BSP removed by tissues outside the liver has been found to be increased whenever the rate of BSP uptake by the liver is reduced,[16] the splanchnic blood flow (ESBF) would tend to be overestimated somewhat more in the hypothermic than in the euthermic dog.

As a consequence, the decrease of liver blood flow with temperature is, if anything, more marked than would appear from the data of TABLE 3A. From these results it may be concluded, therefore, that at 30° C. liver blood flow in these dogs was decreased to a somewhat greater degree than cardiac output. There appears to be no evidence in these data pointing to physical temperature defense by shifting blood flow from the periphery to a body core including the abdominal viscera;[17] it must be remembered, however, that temperature regulation in these animals was at least partially suppressed by the anesthesia employed, and that at 30° C. shivering and other active temperature defenses have fairly well subsided.

An instructive set of results was obtained by studying the removal of $CrPO_4$ radiocolloid from the blood stream by the liver of normal and of hypothermic rats. This material has been suggested as a suitable test substance for the estimation of liver blood flow by analysis of the blood clearance curves.[18] The simplest form of the relation upon which such calculation is based is

$$b = \frac{0.697 \times V_{eff}}{t_{1/2} \times \epsilon} \qquad (1$$

where b is the hepatic blood flow in cc./min., V_{eff} is the extrasplanchni blood volume in cc., $t_{1/2}$ is the half time of disappearance of $CrPO_4$ from the mixed venous blood in minutes (the disappearance curves are very nearly exponential), and ϵ is the fraction of $CrPO_4$ removed from the blood stream in a single passage through the liver. Using the isolated rat liver preparation it can be shown readily that the ϵ in this relation is not a constant, but varies with perfusion rate in the manner shown[13, 19a] in FIGURE 2. The shapes of these curves are determined by three factors: (1) the time of contact between blood and the sinusoidal walls (or, better, the active Kupffer cells in these walls), a variable inversely related to the perfusion rate; (2) the amount of active surface area with which the blood comes in contact in passage through the liver, directly proportional, among other things, to the mean number of parallel hepatic vascular channels through which the blood is flowing actively (see Brauer *et al.*[19a] for more detailed analysis); and (3) the basic rate of the reaction between the colloid micelles and the Kupffer cell surface by which the colloid is removed from the blood stream.

The effect of temperature upon this relation between tissue perfusion and $CrPO_4$ extraction efficiency is shown by the curves of FIGURE 2. At any perfusion rate, the colloid extraction fraction is reduced at lower perfusion temperatures, but the shape of the curves remains virtually unaffected.[1] Since the loss of extraction efficiency with cooling is readily reversible, it was concluded that loss of Kupffer cells is not a factor, but that cooling results in a decrease of the product of the basic reaction rate constant multiplied by active surface area per Kupffer cell. The slopes of the linear portion of the curves of FIGURE 2 are directly proportional to this product, with a Q_1 between 18° C. and 38° C. of 1.92; the same values plotted on Arrhenius coordinates fall on a straight line of slope corresponding to $\mu = 11{,}900$ cal. Further analysis by separation of the reaction rate and specific surface area factors is not possible at the present time.

Injected into intact rats, the same colloid leaves the blood stream at a rate proportional to its instantaneous concentration in the blood, so that blood concentrations decrease very nearly logarithmically with time. The results, therefore, can be conveniently expressed as $t_{1/2}$, half times of disappearance. Very small blood samples suffice for analysis, and repeated measurements in the same rat are possible by the use of this substance; in pentobarbital-anesthetized rats maintained at 38° C. colonic temperature, 3 repetitions of injection and sampling over a 90-min. period yield substantially identical half times of disappearance of $CrPO_4$. Following a base-line determination of $t_{1/2}$ under these conditions, hypothermia was induced by immersing the rats in ice water, and the $CrPO_4$ removal rates were assessed at 1 or 2 subnormal liver temperatures. In a further series this procedure was used to obtain $t_{1/2}$ at 36° to 38° C., and at 29° to 30° C. while cooling was being continued; when these animals had reached 23° C., they were removed from the ice bath, rewarmed between lamps at a rate of 1° C./2 min., and another $CrPO_4$ uptake curve was obtained when liver or colonic temperatures had returned to 29° to 30° C. The results of these experiments are shown in TABLE 3B, together with cardiac output estimates for rats subjected to similar cooling procedures.[20]

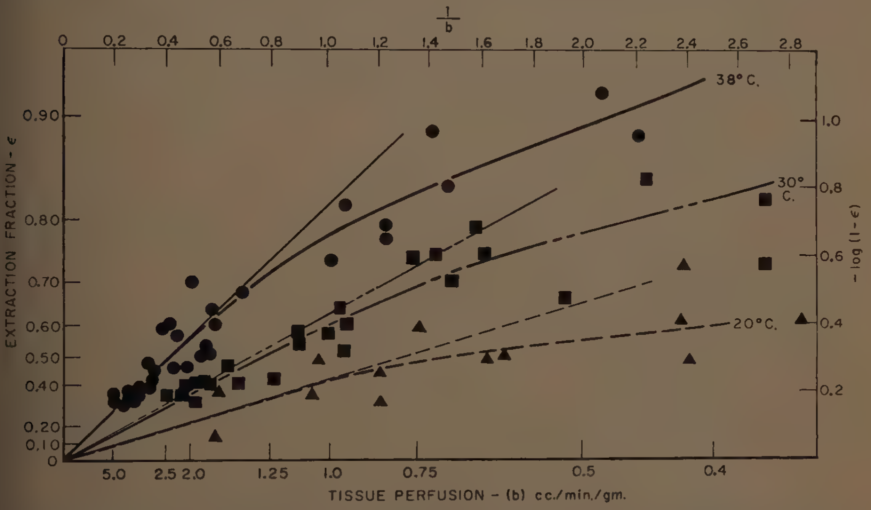

FIGURE 2. $CrPO_4$ colloid uptake efficiency in the isolated rat liver preparation as a function of perfusion rate and perfusion temperature. The coordinates employed are: $-\log(1-\epsilon)$ and $1/b$. Reproduced by permission from the *American Journal of Physiology*.[13]

At first glance these data for the rat might appear to correspond well with the liver blood flow data reported for the dog in TABLE 3A. Actually, however, conversion of the $t_{1/2}$ figures to liver blood flow values requires the use of EQUATION 1 which, in addition to $t_{1/2}$, contains the extrasplanchnic blood volume V_{eff} and ϵ, the extraction efficiency for $CrPO_4$. No data are available to indicate what changes might occur in the extrahepatic blood volume in hypothermia; it seems likely that it would decrease somewhat in parallel with total blood volumes, the changes being of the order of 15 per cent at 30° C Regarding the extraction efficiencies, however, FIGURE 2 allows fairly clea predictions. Cooling will lower the extraction efficiencies at all hepatic bloo flow rates and, at any one perfusion rate, the values of ϵ for several temperatures will be related by ratios that, at perfusion rates above 1.0 cc./gm./min. become nearly constant; using ϵ at 38° C. as unit, these limiting ratios are included as column 5 in TABLE 3B. These resulting values, it will be noted are virtually identical with the ratios of $t_{½}$ at 38° C. to $t_{½}$ for the corresponding

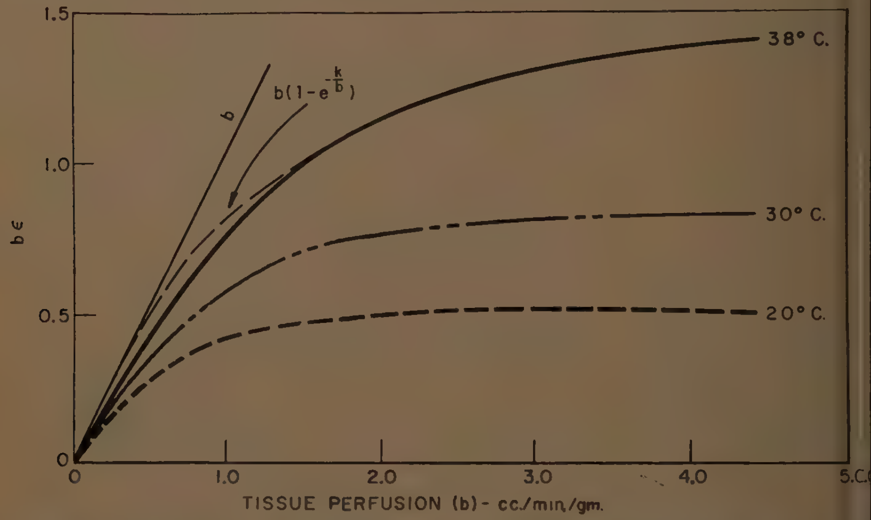

FIGURE 3. Product of tissue perfusion rate and hepatic extraction efficiency for CrPO colloid for the isolated rat liver preparation as a function of tissue perfusion rate and temperature. The light line indicates relations predicted if extraction efficiency were constan and equal to 1.0; the light dashed line indicates predicted values at 38° C. if the hepati vascular cross section were independent of perfusion rates; and the three heavy lines indicate actual results at the temperature shown. Reproduced by permission from the *American Journal of Physiology.*[13]

temperatures. The effect of hypothermia on $CrPO_4$ removal rates in the rat. therefore, is primarily, if not solely, attributable to the temperature dependence of colloid extraction efficiency.

It might be tempting to draw the further conclusion that these result imply that the fraction of the extrasplanchnic blood volume passing th liver in a given time is unchanged in hypothermia even though cardiac output has been reduced by 30 or even by 60 per cent. Such a deduction however, would be fallacious, since it implies that the rate of $CrPO_4$ remova inevitably must vary with hepatic blood flow. Actually, the disappearanc rate of $CrPO_4$ colloid depends, not on the blood flow b, but on the product b of hepatic blood flow times the extraction efficiency ϵ. As shown in FIGURE 3 this product becomes almost independent of liver blood flow when the latte exceeds 1.8 or 2.0 cc./gm./min.; *in vitro*, the product then approaches closel to limiting values which, at different temperatures, are related as the limiting ratios of ϵ, shown in column 5 of TABLE 3B. These ratios, therefore, will measure the ratio of colloid disappearance rates at the corresponding temperatures, regardless of hepatic blood flow rates, provided only that these remain sufficiently large. The $t_{1/2}$ values for 38° C. and for 30° C., shown in TABLE 3B, even on the most conservative assumptions correspond to tissue perfusion rates of 2 cc./gm./min. or more (the 20° C. values are >1 cc./gm./min.), large enough in each case to bring them into the zone of virtual blood flow independence of the clearance curves (the almost horizontal portion of the curves of FIGURE 3). The half times of $CrPO_4$ colloid disappearance for these rats, then, vary *solely* as a function of the limiting ratios of extraction efficiencies, and no conclusions whatever are possible regarding total splanchnic flow.

During rewarming, a somewhat different and all the more interesting picture was obtained. As shown in TABLE 3, at liver temperatures of 30° C. the mean half time for $CrPO_4$ clearance is about 20 per cent greater during rewarming than during the cooling phase of the experiments (the difference probably is real, $p < 0.05$). Examination of the original data reveals that about 40 per cent of the animals tested show very marked retardation of $CrPO_4$ uptake during rewarming, while the remainder show no difference between cooling and warming phases in this respect. In view of the preceding discussion, it seems highly improbable that this difference could reflect changes in total splanchnic flow. Two other factors, however could give rise to the observed change in $t_{1/2}$: a greatly increased extrasplanchnic blood volume during rewarming, or a change in liver blood flow distribution, analogous to that following epinephrine administration, decreasing the number of hepatic vascular channels through which there is an active circulation[19] and leading to a proportional decrease in active surface area presented to the blood stream for $CrPO_4$ uptake. While there is little doubt that changes in blood volume are associated with the induction of and the recovery from hypothermia,[21] it seems unlikely that there should be a 40 per cent difference in blood volume at a given liver or rectal temperature, depending solely upon the direction from which this was approached.

In order to gather direct observations on the possibility of altered blood flow distribution, a series of cinéangiographic studies were conducted. Catheters were placed in one of the tributary veins draining into the portal vein of a series of rats (usually a branch of the ileocolic vein was entered, since this position is compatible with indefinite survival of the prepared rats), and the distribution throughout the hepatic vascular bed of a suitable contrast medium (0.4 cc. of 70 per cent Urokon injected over a period of 4 sec.) was followed by taking motion pictures (35 frames/sec.) of the amplified fluoroscope image (Philips Surgex unit, 65 kv., no accessory filter, 2.5 mAmp.). This procedure could be repeated 3 times in the course of 1 hour in rats maintained at 36° to 38° C. under sodium pentobarbital anesthesia without any indication of significant changes in blood flow distribution with time. When such animals were subjected to cooling by ice packs, slowing of the hepatic circulation was observed. This was slight at 30° C. (about 30 per cent by comparing frame counts in the same animal at 38° C. and at 30° C., using as markers clearly identifiable stages in the distribution of injection mass between catheter tip and the first ramifications of the portal tree) and marked at 20° C. (more than 60 per cent by the same method of estimation). On rewarming, rats fell into 2 groups: 5 of 8 retraced the same stages with little difference between cooling and warming pictures at comparable temperatures Three of 8—about 36 per cent—showed a dramatic change; while during cooling the capillary bed of the entire liver appeared to be evenly perfused

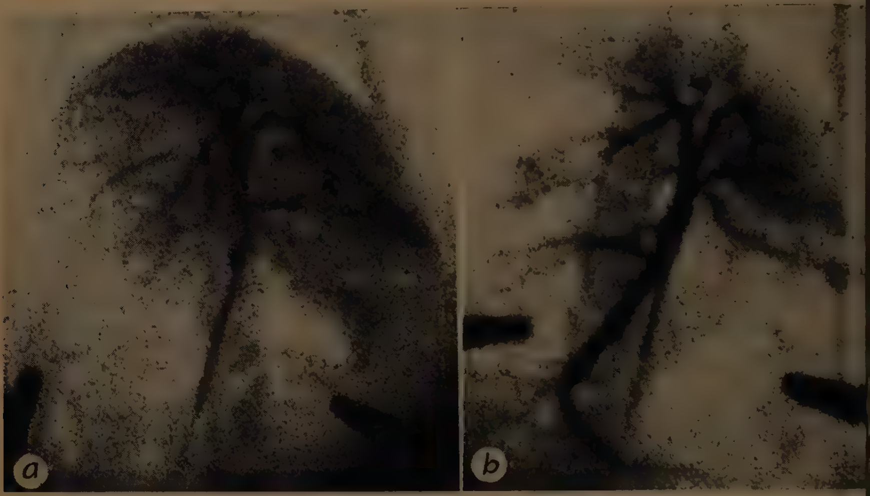

FIGURE 4. Hepatic blood flow distribution in the rat at liver temperatures of 30° C frames from cinéangiograms after 0.4-cc. Urokon injection into the ileocolic vein; th frames represent the instant of maximal major vessel distribution (portogram) immediatel prior to filling of the sinusoidal bed in the regions with active circulation. Legend: (a during cooling; (b) during rewarming after 10 min. at 23° C. (warming rate 1° C./2 min.

and the injection mass had traveled from the injection site directly downstream into the liver, during rewarming in these same animals there wa extensive retrograde flow of the contrast medium, and the hepatogram presented all of the characteristics of a restricted hepatic circulation in the sens of Pritchard and Daniel.[22] These changes are illustrated in FIGURE 4. Th results of these experiments thus are in excellent agreement with the CrPC studies in showing that in about 40 per cent of rats surface-cooled an rewarmed under sodium pentobarbital, the rewarming period is associate with a marked change in the hepatic vascular bed, characterized by restricte blood flow distribution and increased hepatic resistance to perfusion (preliminary results indicate a very similar situation in rats in which hypothermi was induced without barbiturates by the use of the Giaja closed vess technique).

These observations are in line with indications derived from several othe experiments. Studies of the temperature dependence of bile secretion i urethanized rats[23] have revealed differences between bile flow at several subnormal liver temperatures, depending on the direction from which these were approached, cooling giving larger minute volumes at any given temperature than warming. Since bile flow has been shown to be sensitive to liver blood flow distribution changes,[19b] this result would be in keeping with those reported in the present communication. In the hibernating hamster, the active rewarming associated with the awakening sequence was shown to be accomplished with a circulation that is virtually confined to the forepart of the animal, the hindquarters and splanchnic viscera remaining virtually ischemic until the head end of the animal is awake and beginning to move about purposefully.[9b] One may justly inquire whether this may not represent a more fully developed manifestation—in a species specialized for spontaneous hypothermia—of the vascular reflexes underlying the phenomenon seen in 40 per cent of our rats.

The nature of the mechanisms that could underlie these circulatory differences between the animal's losing and regaining body temperatures is as yet obscure. One possibility is that the temperature gradient from periphery to body core, perhaps the skin temperature in particular, is the factor determining the pattern of vasomotor reflexes. Another hypothesis that cannot be disregarded at present is based upon the observation that in dogs the period of rewarming, as well as the first few hours following rewarming after a period of induced hypothermia, is associated with evidence of cardiac decompensation and circulatory embarrassment, which are reversed only gradually.[24] Similar phenomena occurring in the animals discussed above might give rise to circulatory reflexes resulting in restricted visceral blood-flow distribution.

Liver Volume and Fluid Compartments

Some years ago it was shown by stereoroentgenographic methods that the volume of the liver is increased by about 5 per cent on lowering the body temperature of dogs, cats, and rabbits to 30° C., and that further cooling produced little added effect on liver size.[25] The question was posed whether this might not be evidence of a marked increase in liver blood volume. In the isolated rat liver preparation, cooling from 38° to 30° C. produced a similar increase in organ weight, about 4.9 per cent ± 0.2 when perfusion pressures were kept constant (FIGURE 5 and TABLE 4). Cooling to temperatures lower than 30° C. produced little further effect on liver size *in vitro* than *in vivo*.

The increased weight of the isolated rat liver at 30° C. is not due to increased plasma volume, erythrocyte mass, or sodium space in the tissue (TABLE 4). Indeed, the figures of TABLE 4 show that each of these parameters is unchanged or decreased by lowering the perfusion temperature. The weight or volume increase of the liver in hypothermia, therefore, is not due to increased liver-blood volume or to an increase in the volume of fluid occupying the extracellular (or, more precisely the sodium) space of this tissue. The fact that these weight changes are promptly and, after moderate periods of hypothermia, completely reversible on restoring normal tissue temperatures both

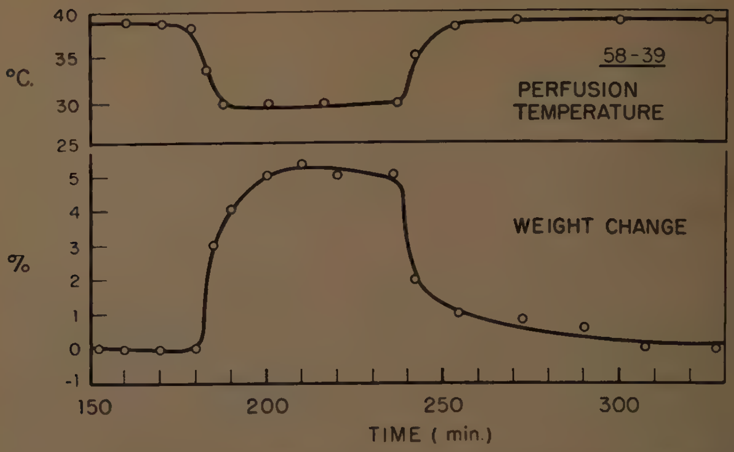

FIGURE 5. The effect of hypothermia on the weight of the isolated, whole blood perfused rat liver preparation (perfusion pressure, 12.5 cm. of blood).

in vivo and *in vitro* is most readily understood if the increase of liver mass the result of fluid accumulation within the tissue. This deduction, togethe with the fluid compartment data of TABLE 4, would best accord with the vie that the entire phenomenon represents a shift of fluid from extracellular t intracellular (or at least nonsodium) compartments. The amount of flui thus shifted would be equivalent to 25 per cent of the normal sodium spac or to 65 per cent of the normal plasma volume, or to 30 per cent of the norma blood volume within the liver, but only to about 7 per cent of the liver ce mass, or 9 per cent of the cell water in the liver.

Such an interpretation would bring these results in line with other observations reported in the literature. Thus, liver tissue tends to swell in solution

TABLE 4

LIVER WEIGHT AND FLUID COMPARTMENT CHANGES IN HYPOTHERMIA

	20° C.	30° C.	38° C.	30°−38° C.
Liver weight* as percentages of 38° C. weight	103.5	104.9	100.0	+4.9 ± 0.2
Plasma volume† as percentages of liver volume (I^{131} HSA)	—	6.9	7.9	−1.0 ± 0.3
Erythrocyte‡ volume as percentages of liver volume (Fe^{59} rbc)	—	5.5	5.5	0 ± 0.4
Na^{24} space (20 min. plasma equiv.)§ as percentages of liver volume	—	23.7	24.2	−0.5 ± 0.3

* Continuous recording for each preparation.
† Single-passage dilution-curve analyses for each preparation.
‡ Scanning for each preparation and tissue analyses.
§ Tissue analyses and scanning for each preparation.
The symbol ± indicates standard error of the mean.

sotonic with blood;[26] the degree of water imbibition by rat liver slices is ncreased by lowering incubation temperatures[10] from 38° to 30° C. *In vivo*, t has been reported on the basis of chloride and thiocyanate distribution olume studies that in hypothermia the calculated intracellular water con- ent of the rat liver is increased from 42.8 per cent at 38° C. through 49.1 per ent during the shivering phase of the induction of hypothermia (33° C.), to 7.2 per cent in deep hypothermia (21° C.).[21] These figures would be in ery satisfactory accord with the other data reported, provided thiocyanate istribution remained unaffected by hypothermia. There is a suggestion in ur data that this fluid shift in the liver is not accompanied by important otassium or glycogen movements, and that it may be associated with a shift f nonelectrolytes into the liver cell (see urea and glucose data below). Since his suggestion, however, at present is based on blood studies alone and not n tissue analyses, it cannot be accepted as more than a tentative hypothesis.

Transfer of Materials Between Blood and Liver Parenchyma

The transfer of substances between the blood stream and the various com- artments of the hepatic parenchyma has been studied in a few scattered nstances only. One of these, the uptake of colloids from the blood stream y the fixed macrophages of the liver, has already been discussed above in ome detail.

As a second example, one might consider the dye sodium phenoltetra- romphthalein disulfonate (BSP). This is a water-soluble dye, taken up argely by the liver cells and secreted into bile after partial conversion to a eries of derivatives.[27a] The relations between perfusion rate and hepatic xtraction efficiency are much more complicated for this substance than for CrPO$_4$ colloid because the uptake reaction itself is partly reversible and because f some coupling between uptake and biliary secretion of the dye.[27b] The elation between blood-flow and extraction efficiency for small doses of BSP n the isolated rat liver at 38° C. is shown in FIGURE 6, together with the imited data available to date to indicate the effect of cooling on BSP extrac- ion efficiency under these conditions. Between 38° C. and 23° C., the fficiency of BSP extraction following single injections of small doses of S^{35}-BSP was reduced at a constant perfusion rate in the Poiseuille region by a actor of 1.9 for each 10° C. fall in perfusion temperature.

In the intact dog continuous infusions of BSP were employed in the meas- urement of ESBF at several temperatures.[14] The extraction efficiency here was found to be low, as is characteristic of the continuous infusion situation, ut it was not changed by cooling. Since, however, the splanchnic blood low rate was reduced at the lower temperatures (TABLE 3A), this observation loes indicate a displacement of the blood flow *versus* extraction efficiency urves in this situation as well. For comparison, these results have been ntered into FIGURE 6 by drawing a horizontal line at the observed constant xtraction efficiency, selecting as the 38° C. point on this line its intercept vith the 38° C. curve describing the rat experiments, and spacing the points or the remaining temperatures at intervals on the blood-flow axis correspond- ng to the appropriate fraction of the 38° C. hepatic blood flow. While the points thus plotted for the hypothermic dog do not coincide perfectly wit the intercepts predicted from the rat perfusion experiments, the agreemen as a whole is quite satisfactory, suggesting that the intact dog shows a temperature displacement of the BSP extraction efficiency/blood-flow rate curve not unlike that of the isolated rat liver.

The real importance of these results, in our opinion, would appear to li in the fact that similar temperature effects were observed under condition in which the distribution of BSP between blood, tissue, and bile differe

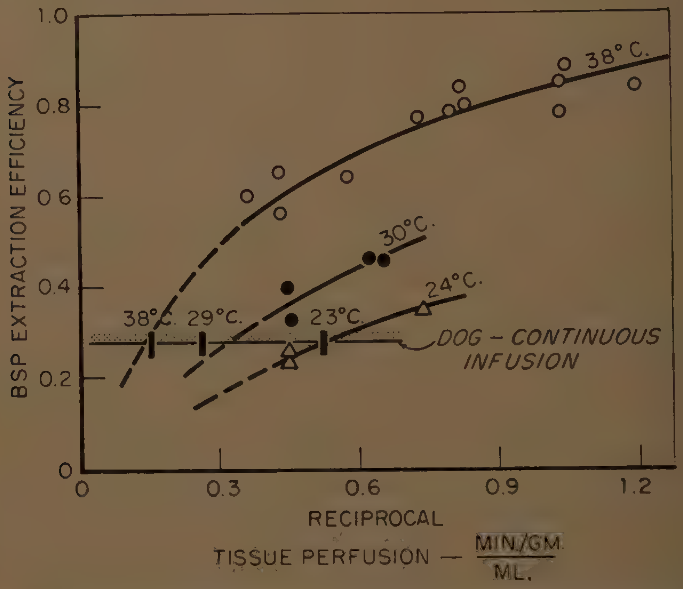

FIGURE 6. Effect of temperature on the relation between tissue perfusion rate an BSP extraction efficiency in the isolated rat liver preparation[7] and in the intact dog (a recalculated).[14]

widely—in the dog, high tissue BSP concentrations, high bile BSP and BS derivative concentrations, and continuous increase of tissue BSP with th passage of time;[16] in the rat, minimal BSP doses, negligible tissue BSP concentrations, and negligible bile BSP levels at the start of each injection Together with the discrepancy between the small temperature effect on BS uptake on the one hand, and the large temperature effect on BSP secretio on the other (to be discussed presently at greater length), these data sugges that the effect of cooling on BSP uptake by the liver is not the result of shift in the blood-tissue equilibria, but rather that it is an expression o slowing of the blood-tissue transfer processes. If this is the correct interpretation, the Q_{10} of nearly 2 would correspond satisfactorily with the view that transfer of this dye is an activated transfer, although not necessaril one requiring the input of metabolic energy.[27b, 28]

The effect of hypothermia on the removal, by the liver, of a few othe ubstances has been described. In these cases, however, data are usually nsufficient to permit even such limited analysis as was possible for BSP and or $CrPO_4$ colloid. Thus, the duration of action of certain barbiturates, uch as sodium Evipal or sodium pentobarbital, is prolonged greatly at reduced ody temperatures, while the effect of other barbiturates such as sodium arbital is not affected to a comparable degree.[29] Since the susceptible arbiturates are inactivated primarily by the liver, these observations have een interpreted as signifying slowing of the rates of removal and of detoxica-ion of these substances by the liver;[30] the relative contributions to this ffect of reduced hepatic blood flow, of retarded blood-to-liver-cell transfer, nd of slowed hepatic metabolism cannot be determined from the data resented. Similarly, it has been reported that hypothermia leads to pro-ongation of the response of the cat's nictitating membrane to injected epi-ephrine, and that warming of the liver region by diathermy reverses this hange; again, hepatic detoxication of injected epinephrine and its delayed etoxication in hypothermia have been invoked to explain these interesting indings.[31] Since the importance of the liver in epinephrine detoxication tself is not entirely established at present, these data may require further tudy before they can be interpreted in terms of an effect of hypothermia on ny aspect of liver function.

The conjugation of morphine and the inactivation of pentothal sodium ave been studied using an isolated rabbit liver preparation, so that the irculatory factor in hypothermia could be eliminated.[11] Marked slowing of oth processes was observed on cooling, nearly in proportion to the reduction f oxygen uptake. Since both of these reactions have been reproduced in ell-free preparations *in vitro*, the effect of hypothermia here possibly could e studied under conditions eliminating changes in transfer rate of substrate rom extracellular to intracellular phase; comparison with the perfusion data hen should permit determination for the detoxications of these substances f the nature of the rate-controlling steps affected by lowering of temperature.

Bile Secretion

A second aspect of the problem of materials transport in the liver is the laboration of bile. The effect of body temperature changes on the volume low of bile was explored some years ago in the urethanized rat.[23] The ptimal temperature was found to be near 40° C.; at temperatures below his value bile flow decreased at a rate corresponding to a mean Q_{10} of 2.15. The values, in general, did not give a good fit on an Arrhenius-type plot, even ver the limited temperature range studied. In any one rat, differences were een in bile flow at each liver temperature during hypothermia, depending pon whether the animal's temperature was being raised or lowered. Higher ile flows generally were observed during the cooling phase than during ewarming. The possible relation of these results to the hemodynamic vents accompanying these temperature shifts has already been pointed out (FIGURE 4).

While the temperature coefficient, Q_{10}, of bile secretion was found[23] to be nly 2.15 for the urethanized rat, it was found to be about 4 in the rabbit during visceral cooling,[32] and between 3.2 and 4.0 for the Sprague-Dawle rat under nembutal/surface cooling[7] from 38° to 28° C.; in the isolated ra liver (FIGURE 7) it ranged from 3.1 to 3.3, the values between 38° and 18° C falling on a straight line on an Arrhenius plot to yield a value for μ betwee 30,000 and 34,000 cal.[33]

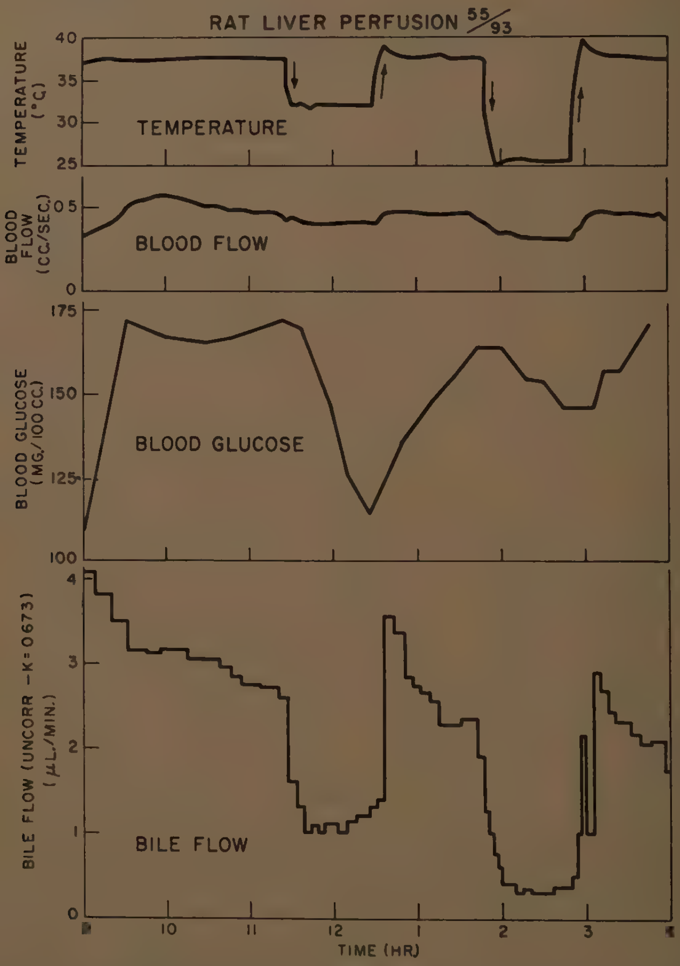

FIGURE 7. Effect of hypothermia on perfusion rate, blood glucose levels, and bile fl in the isolated perfused rat liver preparation. Reproduced by permission from the Nation *Academy of Sciences–National Research Council Publication.*[33b]

In the rabbit studies control experiments were performed to indicate th neither the blood pressure changes observed nor the release of pressor amin could account for the changes in bile flow during hypothermia.[32] In th isolated rat liver the relation between perfusion rate and bile flow was studi at several temperatures (FIGURE 8). Low perfusion temperatures minimi ne blood flow dependence of bile secretion in much the same way as do high xygen pressures[19b] at 38° C. In this sense, hypothermia protects the liver gainst the effects of low perfusion rates and the consequent localized ischemia f certain regions of the hepatic vascular bed. This protection, however, is mited, and severe restriction of hepatic blood flow distribution, either by ery low perfusion rates or by epinephrine administration, will still reduce ile secretion.

In the isolated rat liver, differing in this respect from findings *in vivo*,[18] ver temperature alone defines bile secretion rate; no differences are found at

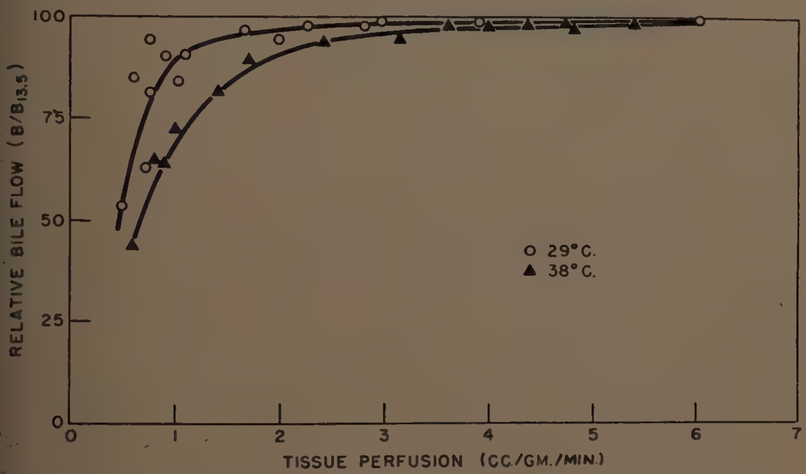

FIGURE 8. Bile flow-blood flow relations for the isolated rat liver, perfused with whole lood at 38° C. and at 29° C.

ny one particular temperature between a given preparation during cooling r during rewarming once steady bile flow levels have been restored. In ontrast to these equilibrium bile flow levels, however, rewarming to 38° C. ften was followed by a brief period of excessively fast bile flow, a bile flow vershoot as it were (FIGURE 7). This could indicate that, somewhere along he chain of metabolic reactions, intermediate products accumulate during ypothermia, giving an extra impulse to bile secretion once normal tempera-ure conditions allowed restoration of metabolic balance.

Choleresis and Bile Composition

In seeking for the rate-controlling reactions responsible for the high-tem-erature coefficient of bile flow, two approaches suggest themselves: examina-ion of changes in bile composition in hypothermia, and consideration of he effectiveness of choleretic agents under these conditions.

Bile salt choleresis is definitely demonstrable both in the hypothermic rethanized rat[22] and in the isolated rat liver.[34] Indeed, more recent experi-ients with the latter preparation have served merely to confirm the earlier bservations in the intact animal. In both cases, either sodium cholate or dehydrocholate is capable of eliciting increased bile volume flow rate i about the same proportion to basal flow rate at 38° C. or at 26° to 28° C. I both cases, also, the time course of the effect is prolonged in hypothermi and the total amount of extra bile produced is reduced somewhat (in a rati of 1:1.3, compared with the euthermic rat[23]). No significant difference wa found in this respect between the choleretic cholate, and the hydrocholereti dehydrocholate, whether these were administered to the intact rat or to th isolated rat liver preparation where the difference in response to these tw agents cannot be attributed to changes in hepatic arterial flow nor, indee to any circulatory factors.[35] There is a suggestion that the overshoot of bi flow on rewarming may be accentuated if the dehydrocholate is administere to the isolated liver during the hypothermic episode; this has not been reporte for the intact animal.

Thus, slow bile flow in hypothermia can hardly result from failure of th liver to respond to choleretic stimuli; the impression is gained, rather, tha choleretic responses are limited by the same factors that limit bile flow i hypothermia in the absence of added choleretic agents. Furthermore, failu to elaborate bile acids and depletion of available stores can hardly be involve in the effect of hypothermia on bile flow: adding such acids to the liver do not appear to be relatively more effective in the hypothermic than in th normothermic organ.

In apparent conflict with this conclusion, it has been observed that sever esters derived from phenymethyl carbinol and related compounds are promp acting effective hydrocholeretics at 38° C. in the rat, but at 26° C. produ only a greatly delayed and, quantitatively, a markedly reduced effect (tot extra volume less than 50 per cent of that produced[23] by same dose at 38° C. These results, however, find their explanation in other observations by th same author proving that these substances must undergo hydrolysis an possibly, still further metabolic change in order to become effective cholere ics. The slowing of these reactions in hypothermia apparently is such th effective drug levels cannot be maintained in the blood stream or in the live This result poses the question whether a similar phenomenon involving som physiological choleretic other than bile salts could not account for th observed effects of hypothermia on bile flow. In the absence of any concre evidence pointing to such a substance, this possibility, for the present, mu be left unexplored and open.

In view of these considerations, it would appear that data are need concerning the effect of hypothermia on the concentrations of the sever conjugated bile acids normally present in bile. Unfortunately, such inform tion is completely lacking in the literature available to us. A suggesti that changes in these bile constituents actually may occur in hypothermia contained in the observation that total solid content is often reduced in bi from perfused hypothermic rat livers (for example, from 2.9 per cent 38° C. to 2.4 per cent at 30° C., or from 2.5 per cent at 38° C. to 2.1 per ce at 30° C.).

Among the remaining bile constituents only certain pigments have bee studied from the point of view of the effects of hypothermia on their secretio

Bilirubin concentrations in the bile of rabbits are not altered by visceral ooling.[32] Thus, the rate of bilirubin secretion remains proportional to the ile flow rate even when, at 28° C., this has been reduced to about 25 per cent f the control value at 38° C. Similarly, in the isolated rat liver preparation ile bilirubin concentrations at 30° C. are increased by only 15 per cent over he corresponding control values at 38° C., even though bile flow rates are educed by about 60 per cent under the same conditions (TABLE 5); total ilirubin secretion rate thus is as greatly reduced in the hypothermic rat iver preparation as in the rabbit.

TABLE 5
SOME BIOCHEMICAL CHANGES DURING HYPOTHERMIA IN THE ISOLATED RAT LIVER PREPARATION

	38° C. Control period	30° C.	38° C. after 30° C. period
Relative bile bilirubin concentration....	100 ≡ 38 μg./ml. ± 4	115 ± 7	166 ± 6
Relative bile bilirubin secretion rate....	100 ≡ 61 μg./100 min. ± 5	53 ± 4	160 ± 4 (or 136 ± 21)*
Relative blood glucose concentration...	100 ≡ 154 mg./100 ml. ± 11	75 ± 10	109 ± 10
Relative blood urea nitrogen concentration	100 ≡ 16 mg./100 ml.	56 ± 15	100 ± 11
Liver glycogen content.............	4.86% ± 0.15	4.59% ± 0.20	—

* Bile flow failed after rewarming in 2 of 8 preparations. The value in parenthesis includes these experiments, while the unenclosed values refer to the results derived from the remaining preparations (± values refer to standard error of the mean).

Rewarming to 38° C., apparently did not affect bile bilirubin concentrations in the rabbit. In the isolated rat liver preparation, as shown in TABLE 5, rewarming invariably resulted in marked increases of bilirubin concentrations in the bile, persisting even after steady bile flow had been restored. Thus, except in the occasional preparations that failed after rewarming, bilirubin-secretion rates persisted considerably above prehypothermia levels. The net extra excretion of bilirubin during the first hour and one half following rewarming (at the end of which time bilirubin secretion in general has returned to prehypothermia levels) roughly compensates for the bilirubin not secreted (retained?) during the hypothermic phase of the experiments. The reason for the discrepancy between the rabbit and the rat liver preparation with regard to bilirubin secretion after rewarming remains obscure at present.

As an example of an exogenous dye secreted into bile in high concentrations, sodium sulfobromophthalein (BSP, sodium phenoltetrabromophthalein disulfonate) has been applied in the study of the hypothermic liver. Secretion of this substance into bile is a rather complex process, associated with transformation of the parent dye into a whole family of derivatives that

TABLE 6
EXCRETION OF BSP AND ITS DERIVATIVES INTO THE BILE OF THE INTACT RAT

	Liver temperature	
	38° C.	30° C.
Peak concentration in bile after 12.5 mg. I.V., mg./100 cc.	810 ±20	738 ±15
Proportion of first 60 per cent of total dye in bile excreted as*		
Compound I	13.9% (12.9 to 16.2)	8.1% (7.8 to 9.0)
Compound II	5.8% (4.4 to 7.2)	6.9% (5.7 to 7.2)
Compound III	80.3% (77.2 to 82.7)	85.1% (85.0 to 85.3

* See Krebs[36] and Krebs and Brauer[27a] for further description of these components.

appear in bile in varying proportions according to the species and the conditions under which the particular liver found itself while excreting BSP.[27a]

TABLE 6 shows the proportions of the three major components in the bil of normal rats following injection of a relatively small dose[36] of BSP.

FIGURE 9 shows the effect of hypothermia on the total excretion of BS in the isolated rat liver preparation. The peak of BSP concentration in th bile occurs slightly later at 29° C. than at 37° C.; there is a marked slowing

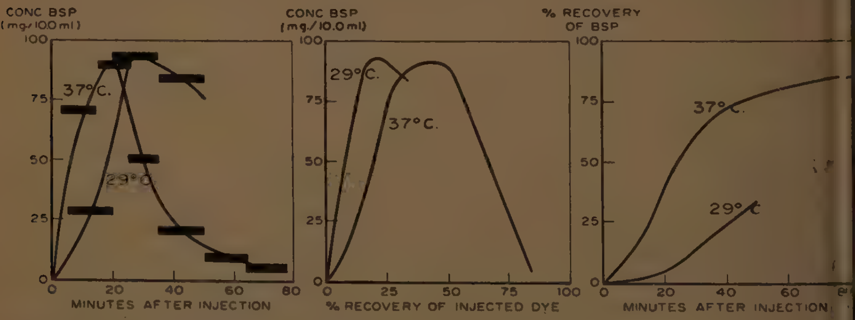

FIGURE 9. Biliary excretion of BSP by the isolated rat liver preparation (55 to 79) 37° C. and at 29° C., and constant perfusion rate.

bile flow (by a factor of about 4). Consequently, the total BSP excretio rate is much slower at the lower temperature, and the bile concentratio peak occurs after less BSP (and BSP derivatives) have been secreted. Th situation *in vitro* is virtually identical with that seen in the intact rat. A shown in TABLE 6, again in the intact rat, at 30° C. bile BSP concentratio reach values close to (possibly slightly below) those attained at colonic temperatures of 38° C.; again the peak occurs slightly later in time at the lowe temperature than at normal temperature, and total bile BSP secretion ra retarded in proportion to bile flow (which in these experiments showed a $_{10}$ of 3.3 to 4.0). Chromatographic analysis of the biles collected from uthermic and from hypothermic rats after BSP administration (TABLE 6) iowed remarkably small dislocation of the BSP transformation mechanism. ndeed, the only difference consists in the slightly more complete conversion f BSP proper (compound I) to compound III, a phenomenon frequently bserved when BSP secretion lags markedly behind BSP removal from the lood (as after larger doses of the dye). Thus, like the bilirubin secretion, he biliary secretion of BSP on the whole appears to be impaired in hypohermia only to the extent that bile flow rates are reduced; bile concentrations nd metabolic transformation of the dye remain virtually unaffected.

Taken together, the bile flow overshoot, the extra bilirubin secretion, and he bile retention pattern of BSP components in hypothermia bile suggest he possibility that hypothermia induces a state of physiological bile stasis in he liver. Such an effect would not be out of line with the discrepancy etween the rather large temperature coefficient of bile secretion rate (Q_{10} of to 4) and the smaller temperature coefficients (approximately 2) for various ther phases of liver metabolism. More remarkable than modification of bile ecretion in hypothermia, however, is the fact that despite very large differnces in secretion rate, bile composition suffers only rather minor changes. 'hus, the liver seems to possess homeostatic mechanisms capable of maintainng nearly constant bile composition in the face of conditions that might be xpected to unbalance drastically the various phases of liver metabolism and o alter greatly the chemical composition of liver cells, as well as of liver cell ecretions.

Hypothermia and Liver Metabolism

The effect of suboptimal temperatures on oxygen consumption by liver issue was reviewed briefly in connection with the discussion of thermoenesis. All observations seem to be in accord with a Q_{10} of about 2 for iver oxygen consumption[10, 11] over the range from 38° to at least 20° C. t is far from permissible, however, to deduce from this that energy producion is halved by a fall of 10° C. in liver temperature. On the contrary, here are indications that in hypothermia the source of metabolic fuel is hanged, fat combustion being encouraged at the expense of carbohydrate netabolism. Thus, in the hibernator during the hypothermic phase, the RQ drops to very near 0.70, and fat depots are depleted while blood glucose nd liver glycogen remain at normal or even high levels.[9] Fatty livers are ommon under these conditions. In nonhibernators direct comparisons of lood or liver carbohydrate stores in euthermic and in hypothermic subjects re rendered difficult by the intense carbohydrate utilization associated with emperature defense during the induction of hypothermia. However, there gain the RQ falls with the body temperature so that at 27° C. (colonic emperature) the RQ of rabbits did not differ significantly[37] from 0.70.

In the isolated rabbit liver a similar but more transient fall of RQ was eported,[11] raising the possibility that incomplete gas equilibria rather than ntrinsic changes in CO_2 production rate might account for the effect *in vitro*.

In a more direct approach to the presumptive effect of hypothermia carbohydrate metabolism, blood glucose analyses have been performed. the isolated rat liver, blood glucose levels decrease with cooling, and retu to normal or slightly elevated levels when the preparations are restored 38° C. (TABLE 5). As shown in FIGURE 7, the extent of this hypoglycem does not bear a simple relation to temperature but, like the weight change is greater at 30° than at 20° C. The change in liver glycogen content th would correspond to the glucose lost from the perfusate is not large enoug to be assessed with assurance; indications are, however, that hypotherm does not regularly elicit an increase in liver glycogen content (TABLE 5 Since blood urea levels decrease in much the same way as blood glucose leve in hypothermia in the isolated rat liver preparation, and since the extent these shifts parallels the weight changes in the organ, it appears permissib to speculate that these nonelectrolyte solutes might enter the liver cells alon with the fluid shifted from extra- to intracellular compartments. In an case, the glucose plus urea lost from the circulation at 30° C. are osmotical equivalent to blood plasma amounting to about 6 per cent of the liver weigh Since the amount of fluid actually taken up is 4.9 per cent of the liver weig (TABLE 4), the correspondence is at least suggestive. (Incidentally, assumin that this glucose went into liver cells as glycogen, and assuming that 2.3 gr of water is carried into the cells with each gram of glycogen,[38] the calculat weight increase between 38° C. and 30° C. amounts to a mere 1 to 1.3 per ce of the liver weight, so that this assumption would not account for the effe of hypothermia on liver volume.)

In the intact animal a careful series of studies concerning the effect hypothermia on carbohydrate metabolism has been reported.[37, 39, 40] Whi these studies were not specifically concerned with the role of the liver in t changes observed, they are sufficiently suggestive to appear relevant in th place. In man, dog, and rabbit alike, hypothermia results in marked flatte ing of the glucose tolerance curves.[39] So great is this effect at 27° C. colon temperature, that the question was posed whether such a degree of hyp thermia might not block glucose utilization altogether. If this were to resu in a shift of metabolism resulting in the exclusive combustion of fat, t observed RQ of 0.70 would be accounted for satisfactorily.[37] Fructo tolerance curves were far less affected by cooling; fructose administrati caused the appearance in the circulating blood of glucose in amounts appro mately equivalent to the fructose removed.[40]

These communications were followed by a critical study, employing n only RQ, blood glucose, and glucose tolerance curve data, but also includi measurements of A-V glucose differences, urinary spillages, and estimates the extracellular fluid compartment.[37] This further work indicated tha while glucose utilization is probably retarded in hypothermia, it is not co pletely abolished even at colonic temperatures below 30° C.[37] The respon of glucose oxidation to insulin appears to be virtually nil in the hypotherm rabbit, and the effect of insulin on glucose distribution was found to reduced, although not eliminated. On the basis of their experience, the authors emphasize that blood analyses alone, in whatever form, cann rovide sufficient data to justify any conclusions regarding the status of the arbohydrate metabolism in the hypothermic subject.

A final observation that may have a bearing on carbohydrate metabolism n hypothermia is the report, based on histochemical examination only, that ver glycogen content remains unchanged during the first three or four hours f hypothermia in the dog, but that it declines thereafter, even as histo-athological change becomes evident in the tissue.[41]

Nitrogen metabolism has not been explored in hypothermia except for the bservation that, in the hibernating hamster, plasma protein levels remain irtually constant and for a few observations on urea concentrations in the lood perfusing the isolated rabbit[11] or rat liver (TABLE 5). The rate of urea ncrease was markedly retarded in both situations. In addition, in the rat he solute shift already discussed in connection with the glucose experiments esulted in a marked decrease of blood urea levels during the hypothermic eriod (TABLE 5). As before, in the absence of tissue analyses or balance tudies, the effect of hypothermia even on gross nitrogen metabolism must e considered as unexplored at the present time.

All told, the information on liver metabolism in hypothermia appears to e very meager. There is a suggestion in all of the available results that the islocation of liver metabolism and liver composition is remarkably slight n hypothermia and, consequently, that homeostatic mechanisms must come nto play to maintain chemical integrity of the tissue for limited periods in he nonhibernator and for virtually unlimited periods in the hibernator, so hat essential functions are carried on even in the hypothermic organism nd so that recovery can take place, leaving but a minimum of scars upon the issue. It would seem that a most promising field of investigation should be ound in the exploration of the metabolic balance established under these onditions, using those many modern methods of metabolism study which, trangely enough, have not been applied to this problem to date.

Histological Changes

Two lines of evidence may be mentioned that support the view that the ypothermic liver can find a new metabolic and structural equilibrium of emarkable, although not perfect, stability.

Histological examination of tissues from hypothermic animals, in general, ave emphasized the small extent of pathological changes in the livers even f subjects exposed to prolonged hypothermia. In most of the earlier studies, esults are complicated by uncertainty regarding the degree of anoxia accom-anying the hypothermia.[42] The watery vacuoles and evidence of increased ell volume may be attributed either to anoxia or to such changes in tissue luid balance as were described for hypothermic liver slices or perfused liver n an earlier section of this report. More recently, visceral cooling methods ave permitted reducing liver temperatures while minimizing the circulatory hanges associated with severe generalized hypothermia.

In such experiments on rabbits, structural changes in the tissue in general vere slight during the first 2 or 3 hours at 25° to 30° C., and thereafter ncreased rather rapidly with the lapse of time.[41] The most frequently observed abnormality consisted, once again, of watery vacuoles appearin in the cytoplasm of the hepatic cells; on rewarming, the histology of th livers of these animals had returned to normal after 24 hours. Liver glycoge in these same subjects began to fall below the levels of anesthetized contr rabbits after about 2 hours of hypothermia. We attribute these vario results primarily to insufficient oxygen supply to the liver (although direct evidence in support of liver anoxia is presented), but call attention the fact that occasionally vacuolization of the parenchymal cell cytoplas is seen at a very early stage of the cooling process, suggesting that tiss hypothermia may, after all, be a contributing factor.

Another possible source of pathological changes in the livers of anima subjected to several hours of moderately profound hypothermia has bee described as the basis of studies on dogs subjected to surface cooling und pentobarbital anesthesia.[43] Numerous small focal necrotic lesions, togeth with congestion of the abdominal viscera and ascitic fluid accumulatio were observed after recovery. The suggestion is made that these chang could well reflect an increased tendency toward erythrocyte agglutination hypothermia, resulting in the formation of microemboli which could produ the kind of circulatory embarrassment indicated by the pathology recorde

More dramatic than this evidence of low-grade cold-induced liver patholo is the fact that hypothermia can greatly reduce the deleterious effect on t liver of visceral ischemia. This might be anticipated for hepatic ischem alone on the basis of the observation, reported above, that bile flow *in vit* can be maintained at far lower perfusion rates when liver temperatures a 29° to 30° C. than when they are 37° to 38° C. (FIGURE 8). In the inta animal aortic occlusion as well as occlusion of the afferent blood supply the liver results in severe liver damage if the period of ischemia excee 20 min. at 35° to 37° C.; in the hypothermic dog, on the other hand, far mo extended ischemic periods can be tolerated with minimal functional or stru tural liver injury.[44] It has since been shown that the deaths occurring the normothermic subjects under these conditions cannot be prevented b arterialization of the liver or by cooling of the liver alone,[45] so that it must concluded that injury to the intestinal tract, rather than to the liver, is t primary cause of death and is the site protected by hypothermia. T liver lesions also were minimized in the hypothermic subjects, and it is n clear whether these lesions were the result of hepatic anoxia, and hen directly minimized by cooling of the tissue, or whether they were secondary the shock that resulted, in turn, from the intestinal injury. Indeed, we conc with the conclusion of Shumway and Lewis[46] that "resistance of the liver ischemia is difficult to assay. The problems of 'neighborhood' effects in dent to the vascular occlusion necessary for rendering the liver ischemic te to take priority over the hepatic response and make it next to impossib to assess *in vivo* the direct protection afforded the liver by hypothermia und these conditions."

The ability of the liver to retain its functional competence after extre exposure to hypothermia, however, may be demonstrated by a combinati of *in vivo* and *in vitro* techniques. If rats are subjected to severe cooling f xtended periods of time, experience has shown that resuscitation by present nethods is not feasible. However, when livers from such animals are esected and transferred to a perfusion circuit, normal or near-normal liver unction can be restored quickly and, apparently, can be maintained for as ong as in any other isolated rat liver. FIGURE 10 illustrates three such xperiments, of which only the third gives evidence of recovery of seriously leranged liver. In this case, however, at least 30 per cent of the liver itself vas frozen; there was evidence of extensive tissue damage involving, apparntly, the endothelial lining of the sinusoids and small vessels to a particuarly severe degree.

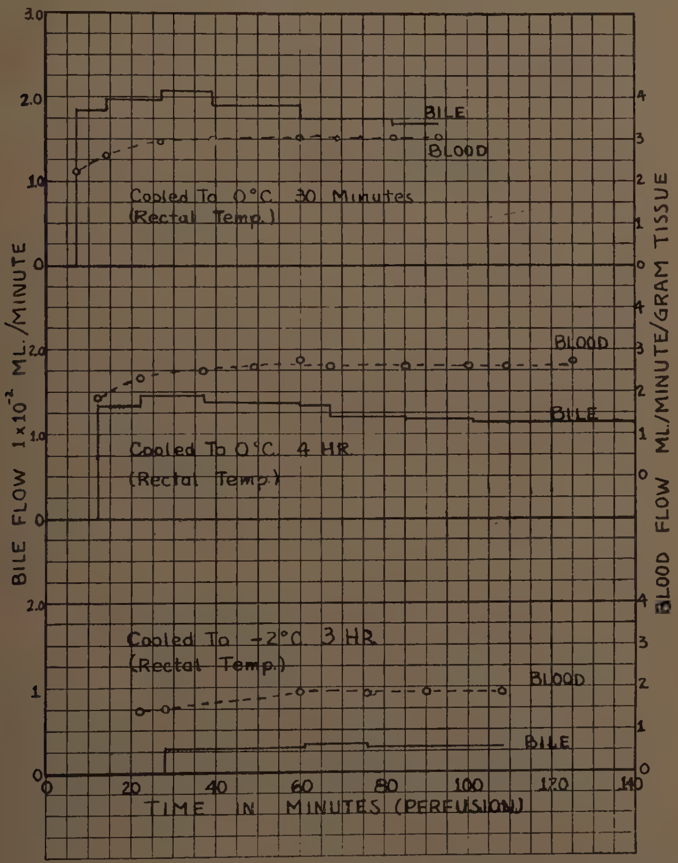

FIGURE 10. Perfusion of livers from rats exposed to prolonged, extreme hypothermia; ile flow and blood flow rates. Reproduced by permission from the *National Academy f Sciences–National Research Council Publication.*[33b]

These experiments are quoted at the end of this paper since they lead from he realm of work accomplished to the realm of work to be accomplished. Nearly twenty-five years ago Barcroft, in reviewing the information then

TABLE 7
BALANCE SHEET OF INFORMATION ON HYPOTHERMIA OF THE LIVER

	Assets	Liabilities
Thermogenesis	Liver contributes constant fraction of BMR in normal and in cold-adapted animals. Liver is not essential to extrathermogenesis during temperature defense or recovery.	Measurements of liver or splanch nic O_2 uptake and RQ durin various phases of a cycle of in duced hypothermia and recovery
Circulation	Estimated splanchnic blood flow decreases more than cardiac output in hypothermia. There is a decrease of hepatic resistance *in vitro* during hypothermia. In 40 per cent of rats rewarming is accompanied by restricted blood flow distribution in liver and increased hepatic resistance.	Simultaneous measurements c cardiac output and splanchni blood flow during hypotherm cycle. Studies on nature of reflexes dur ing rewarming that give rise t restricted circulation, and o relation of this to circulation em barrassment in subjects recove ing from hypothermia.
Liver volume	Increased by approximately 5 per cent due to fluid shift to intracellular compartment.	Documentation of solute di tribution by direct blood an tissue analyses.
Blood clearance and detoxication	$CrPO_4$ colloid uptake, $Q_{10} = 1.92$; change not due to decreased Kupffer cell numbers. BSP uptake efficiency halved by 10° C. cooling, apparently due to slowing of blood-liver cell transport. Barbiturates, morphine, epinephrine all handled less rapidly by hypothermic liver.	Experiments to separate hypo therms effect on transmembra transport from effects on detox cation and subsequent handlin
Bile secretion	Bile flow, $Q_{10} \simeq 3.5$ between 38° and 18° C. Effect of low liver blood flow rates on bile flow is much less at 28° than at 30° C. Overshooting of bile flow on recovery from hypothermic period. Choleretic drugs as effective, proportionately, at 28° as at 38° C., unless metabolic conversion to active form is required. Bilirubin concentration, at most, is slightly higher in hypothermic bile than in euthermia. Overshooting of bilirubin concentration in bile on recovery from hypothermia. BSP concentrations and proportions of BSP components in bile substantially unaffected by hypothermia.	Follow-up suggestion from ove shoot observations that met bolic deficit of a sort accum lates during hypothermia; is th related to discrepancy betwee Q_{10} of 3.5 for bile flow and Q_1 about 2 for most other processe

TABLE 7 (*Continued*)

	Assets	Liabilities
Metabolism	Oxygen consumption, $Q_{10} \simeq 2$. Whole body data suggest decreased glucose utilization, increased fat utilization, no interference with fructose utilization. Perhaps slowing of urea production. Hepatic glycogenolysis during rewarming phases of hypothermia cycle. Solute shifts involving at least glucose and urea complicate blood analyses.	Metabolic studies on isolated tissue, what adjustments between different reactions underlie metabolic equilibria in hypothermia? Can metabolic drift be documented?
Pathology	Slight and reversible changes in general, cytoplasmic vacuoles, glycogen depletion after protracted hypothermia. Protection against liver injury due to hepatic ischemia: interpretation complicated by effects on other splanchnic viscera. Recovery of liver function possible after prolonged exposure of whole animals to lethal levels of hypothermia if liver is then isolated and perfused.	Follow-up indications that time factor is of essence in damaging liver tissue during hypothermia. Is this metabolic drift or structural breakdown?

available regarding temperature effects on biological systems, stated: "It is surprising enough that at any one temperature all reactions of the body should progress at velocities suitable to one another."[47] His statement well describes the impression gained from the more recent experiments here reviewed. However, it must be apparent from the data discussed that, in addition to the general adequacy of the new homeostasis established in the hypothermic tissue, the stubborn fact remains that these new equilibria are only relatively stable, that viable tissue turns to inviable by a slow but inexorable drift, and that metabolic unbalance and structural changes accumulate in time to the point where recovery on rewarming of the cooled tissue no longer is possible. It is in the exploration of these processes that limit survival of the homeotherm at low temperature that the next major contribution of organ physiology to the understanding of hypothermia is most likely to be made.

Summary

It appears to us that the substance of this communication is best summarized in the form of a table listing, in the most cryptic form, topics, established conclusions, and the many wide gaps uncovered by this review of current knowledge in this field. Accordingly, this summary appears in the accompanying TABLE 7.

Acknowledgment

We thank E. L. Dobson, Donner Laboratory, University of California, for providing the $CrPO_4$ colloid preparations employed throughout this work.

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THE EFFECT OF HYPOTHERMIA ON RENAL FUNCTION AND RENAL DAMAGE FROM ISCHEMIA

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Hypothermia has been useful in the prevention of tissue damage during periods of ischemia. Employment of this technique requires that (1) the effect of hypothermia be observed, and (2) the ability of the hypothermia to prevent tissue damage be studied. With this thought in mind, the renal effects of hypothermia with and without ischemia were studied. The kidneys were used as the tissue to be studied since it is possible numerically to assess the functional capacity of the kidneys and to evaluate the severity of residual renal damage that occurs as a result of the hypothermia and/or ischemia.

METHODS

Effect of Hypothermia Alone

Laboratory observations. The effects of hypothermia alone were observed in two groups of dogs. Observations were made on renal hemodynamics and

TABLE 1

EFFECT OF PROGRESSIVE REDUCTION IN BODY TEMPERATURE ON RENAL HEMODYNAMICS AND WATER AND ELECTROLYTE EXCRETION

	Body temperature 37° C. Observation (control)	Body temperature 32° C.		Body temperature 29° C.		Body temperature 27° C.	
		Observation	p* value <	Observation	p value <	Observation	p value <
Mean blood pressure, mm. Hg	114	100	0.05	96	0.05	86	0.001
Glomerular filtration rate, cc./min	36	21	0.001	16	0.001	11	0.01
Renal plasma flow, cc./min.	118	79	0.05	49	0.01	32	0.01
Hematocrit	38	38	NS	39	NS	38	NS
Urine volume, cc./min	0.7	1.0	NS	1.0	NS	0.9	NS
Plasma sodium, mEq./l.	141	140	NS	141	NS	144	NS
Plasma potassium, mEq./l.	3.1	2.6	NS	2.7	0.10	2.7	NS
Urine sodium, μEq./min.	68	60	NS	82	NS	71	NS
Urine potassium, μEq./min.	24	24	NS	20	NS	15	0.10

* $p - t = \bar{x}\sqrt{\frac{n(n-1)}{S_x^2}}$.

NS = p Value > 0.10

TABLE 2

EFFECT OF PROLONGED HYPOTHERMIA ON RENAL FUNCTION

	Control	Hypothermia immediate (27° C.)		Hypothermia 1 hour (27° C.)		Normothermia	
		Observation	p value <	Observation	p value <	Observation	p value <
Mean blood pressure, mm. Hg	120	79	0.001	79	0.001	114	NS
Glomerular filtration rate, cc./min	48	16	0.001	19	0.001	33	0.01
Renal plasma flow, cc./min.	160	51	0.001	53	0.001	110	0.001
Hematocrit	38	43	0.05	43	0.05	43	0.05
Urine volume, cc./min	0.7	0.7	NS	0.9	NS	1.2	0.10
Plasma sodium, mEq./l.	135	137	NS	137	NS	135	NS
Plasma potassium, mEq./l.	3.1	2.6	0.05	2.4	0.01	2.9	0.30
Urine sodium, μEq./min.	35	51	NS	54	NS	47	NS
Urine potassium, μEq./min	24	14	0.05	14	0.05	26	NS

TABLE 3

RENAL EFFECTS OF HYPOTHERMIA IN MAN

	Control	Anesthesia alone		Anesthesia and hypothermia	
		Observation	p value <	Observation	p value* <
Mean blood pressure	103	98	0.20	90	0.10
Glomerular filtration rate, cc./min	96	86	NS	64	0.10
Renal plasma flow, cc./min	594	527	NS	349	0.001
Hematocrit	43	42	NS	44	NS
Urine volume, cc./min	1.2	1.5	NS	2.6	0.05
Plasma sodium, mEq./l.	144	144	NS	146	0.10
Plasma potassium, mEq./l.	4.4	4.4	NS	4.1	0.001
Urine sodium, μEq./min	140	144	NS	128	NS
Urine potassium, μEq./min	61	59	NS	36	0.05

* Statistical analysis using period after anesthesia for comparison.

on water and electrolyte excretion. Details of the technique have bee reported previously.[1, 2] Creatinine was used to measure glomerular filtratio rate; para-aminohippurate was employed to measure renal plasma flow Electrolyte determinations were made with a Beckman flame photometer.

The animals in group 1 were used to study the acute effects of progressiv reduction in body temperature. The observations are recorded in TABLE 1

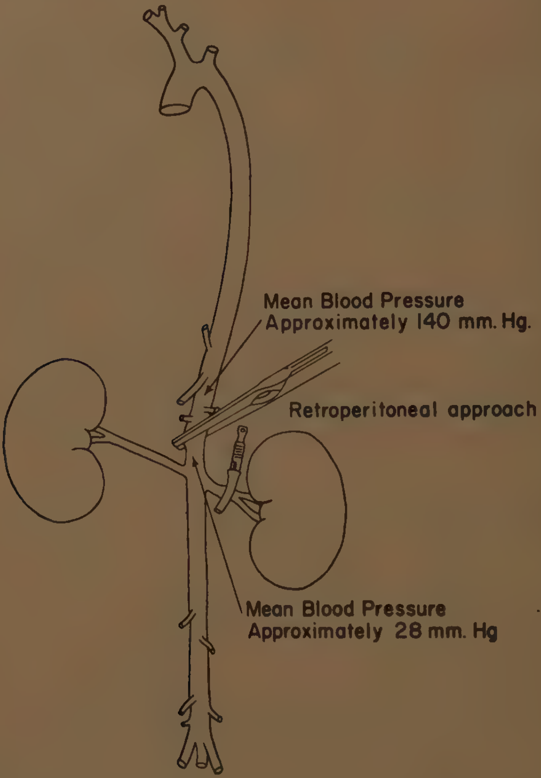

FIGURE 1. Sites of combined occlusion of the aorta and one renal artery to compar renal response to ischemia during the normothermic and the hypothermic states.

Group 2 consisted of animals in which the renal effects of prolonged hypothermia at approximately 27° C. were observed. The observations ar presented in TABLE 2.

Observations in man. Observations on renal hemodynamics and on wate and electrolyte excretion were made on 3 women and 8 men. Inulin wa used to determine glomerular filtration rate, and para-aminohippurate t determine renal plasma flow according to techniques described previously All patients were anesthetized. The observations are summarized in TABLE

Effect of Hypothermia on Renal Damage from Ischemia

The second part of the studies concerned the ability of hypothermia t prevent tissue damage resulting from ischemia. For these experiment observations were made on two additional groups of dogs. Control observations on renal function were made on these animals as described previously,[3, 4] observing renal function in the right and left kidneys individually and simultaneously. The effect of renal ischemia under normothermic conditions was studied in the animals in group 3. The aorta above the origin of the renal arteries and the left renal artery were occluded simultaneously for a period of three hours (FIGURE 1). The dogs were then allowed to recover from anesthesia and were returned to their cages. Renal damage was estimated 3 days later by repeating the renal function studies, as they were done during the control period.

Table 4

Renal Damage Resulting from Renal Ischemia Under Normothermia as Compared to Hypothermia Conditions

	Glomerular filtration rate, cc./min.	Renal plasma flow, cc./min.	Sodium excretion, μEq./min.
Normothermic when renal artery occluded			
Occluded kidney			
Control	23	73	34
Experimental	1	4	6
Observation p value <	0.001	0.001	NS
Unoccluded kidney			
Control	23	73	34
Experimental	20	89	32
Observation p value <	NS	NS	NS
Hypothermic when renal artery occluded			
Occluded kidney			
Control	23	82	77
Experimental	20	65	111
Observation p value <	0.05	NS	NS
Unoccluded kidney			
Control	23	82	77
Experimental	28	90	35
Observation p value <	NS	NS	NS

NS = p Value > 0.10, which is not statistically significant.

Control observations were made on the animals in group 4 similar to those made on the animals in group 3. These animals were then anesthetized and the temperature reduced to 27° C. The aorta and left renal artery were occluded simultaneously for 3 hours, as on the animals in group 3. The animals were then allowed to recover and were returned to their cages. Three days later renal function was determined as during the control period. The observations are recorded in TABLE 4.

RESULTS AND COMMENTS

Effect of Hypothermia Alone

Laboratory observations. In TABLE 1 are detailed the effects of progressive reduction of body temperature on renal hemodynamics and on excretion of water and electrolytes. It will be noted that, as the body temperature was reduced to 27° C., there was a progressive reduction in mean blood pressure from an average of 114 mm. Hg for the control values to 86 mm. Hg ($p < 0.001$). This represents a 25 per cent reduction in mean blood pressure. Associated with the reduction in blood pressure, there was a marked reduction in glomerular filtration rate from an average of 36 ml./min. to 11 ml./min. ($p < 0.01$), a reduction of 69 per cent.

TABLE 5
COMPARISON OF RESPONSE IN WATER EXCRETION WHERE THE GLOMERULAR FILTRATION RATE IS REDUCED BY VARIOUS METHODS

	Hypothermia		Norepinephrine		Hemorrhage	
	Control	Experimental	Control	Experimental	Control	Experimental
Mean blood pressure, mm. Hg	114	86	131	195	131	54
Glomerular filtration rate, cc./min.	36	11	56	32	50	20
Urine volume, cc./min	0.7	0.90	2.1	1.5	2.0	0.7
Sodium excretion, μEq./min	68	71	136	69	183	12

Associated with the reduction in glomerular filtration rate, there was a parallel reduction in renal plasma flow ($p < 0.01$). The hematocrit was not affected. The depression in renal function in these animals was a progressive one that paralleled the decrease in body temperature.

Although the glomerular filtration rate was markedly reduced, this was not associated with a decrease in urinary volume ($p > 0.10$) nor in a significant decrease in sodium excretion ($p > 0.10$). This is remarkable in that, under normothermic conditions, any manipulation that reduces the glomerular filtration rate to this extent will greatly depress urinary volume and excretion of sodium (TABLE 5). Excretion of potassium was depressed to a degree that approached statistical significance ($p < 0.10$). It would appear that the tubular enzymatic reabsorptive mechanism is depressed; therefore, the reabsorption of sodium and water is apparently reduced. On the other hand excretion of potassium by the tubules is an active process and, by the same reasoning, the urinary excretion of potassium was reduced by hypothermia. There was no significant effect on plasma sodium, but the plasma potassium decreased slightly, although this response was not statistically significant (TABLE 1).

When the temperature was maintained at 27° C. for one hour or more (TABLE 2), there was not a progressive reduction in blood pressure, glomerular filtration rate, or renal blood flow; instead, these functions remained constant. These functions were depressed to the same extent immediately as they were after one hour. This indicates that the reduction in blood pressure and renal function is a direct result of the degree of hypothermia rather than one related to the period of time that the temperature remains reduced. Similar deductions can be made relative to the effect of prolonged hypothermia on urinary volume and sodium excretion in that the observations after one hour of hypothermia were similar to the observations made immediately after maximum reduction in body temperature to 27° C.

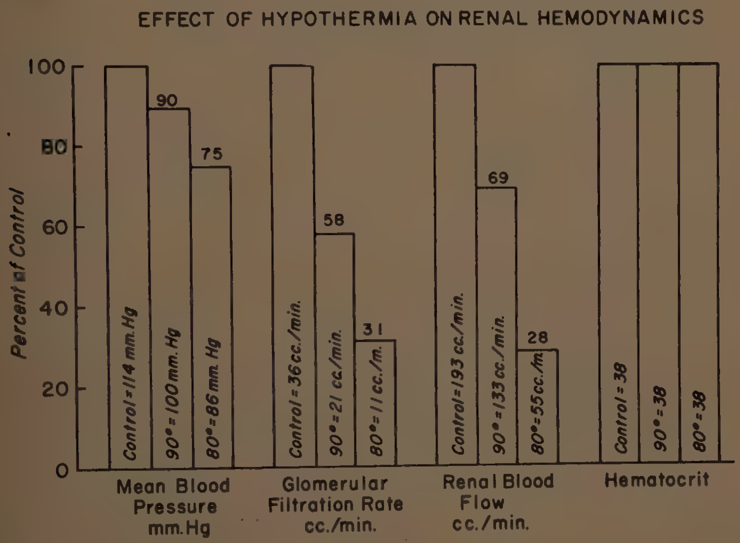

FIGURE 2. Effect of progressive reduction in body temperature on renal function. Glomerular filtration rate and renal blood flow decreased progressively.

When the temperature was returned to normothermic levels, the blood pressure for the group returned to approximately the same value that existed prior to the induction of hypothermia (TABLE 2). However, the glomerular filtration rate did not immediately return to control values, but increased only to 69 per cent of the control values ($p < 0.01$), as contrasted to 33 per cent of the control value during maximum hypothermia. Likewise, renal blood flow returned only to 70 per cent of the control values ($p < 0.01$), as contrasted to 35 per cent during maximum hypothermia.

When the body temperature increased there was a moderate increase in water excretion. The excretion of sodium after return of body temperature to normal was 134 per cent of the control value. The excretion of potassium returned to 108 per cent of the control value ($p > 0.50$) as contrasted to 59 per cent of the control during maximum hypothermia ($p < 0.05$). The concentration of sodium in the plasma was not altered following a return of bod temperature to the normothermic state, but the plasma potassium increase from 2.6 mEq. to 2.9 mEq., an increase of 11 per cent in the normotherm state as compared to maximum hypothermia.

When the mean blood pressure was increased with the infusion of norepi nephrine to the control value in 20 dogs (FIGURE 3), the depressed rate o glomerular filtration and renal blood flow was not improved ($p > 0.50$) Neither urinary volume ($p > 0.50$) nor excretion of sodium ($p > 0.50$

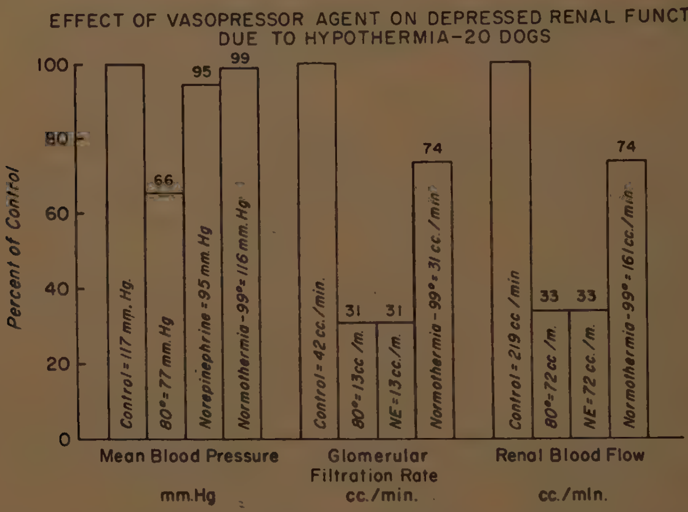

FIGURE 3. Effect of increasing the blood pressure with norepinephrine during hypothermia. As the blood pressure was increased, glomerular filtration rate and renal bloo flow were not altered. There was a sharp increase in these modalities when the body temperature was returned to normal.

increased. As a matter of fact, there was a slight reduction in sodium excretion following the infusion of norepinephrine from 88 per cent of the contro value for this group of animals to 71 per cent which, however, was not statistically significant. These observations seem to indicate that the depressio in renal function was not a result of the hypotension, but that, instead, i was related to the hypothermic state.

As the rate of glomerular filtration (GFR) and renal blood flow decrease during hypothermia in a small group of animals thus studied, there was a parallel reduction (FIGURE 4) in maximum tubular function (TmG). Usually the GFR/TmG ratio increased due to a somewhat greater reduction in maximum tubular function than in glomerular filtration rate, apparently a result of enzymatic inhibition.

Observations in man. The observations in man parallel the observation made in the laboratory. As anesthesia was induced, there was frequently a slight reduction in mean blood pressure. As the temperature decreased in anesthetized man, there was usually an additional reduction in mean blood pressure. The average mean blood pressure for the group decreased from 98 mm. Hg to 90 mm. Hg ($p < 0.10$). This was associated with a significant reduction in glomerular filtration rate (74 per cent of control), comparing the control values (after anesthesia induction) to the hypothermic values. The renal blood flow paralleled the rate of glomerular filtration, but the depression was more marked.

Hypothermia did not appear to affect the hematocrit. This, again, was quite similar to the results observed in the laboratory animal. Excretion of sodium was not altered significantly and excretion of potassium decreased ($p < 0.05$). Although the concentration of sodium in the plasma was not altered, the concentration of potassium decreased ($p < 0.001$), which may have been due, in part, to the intravenous infusion of fluids.

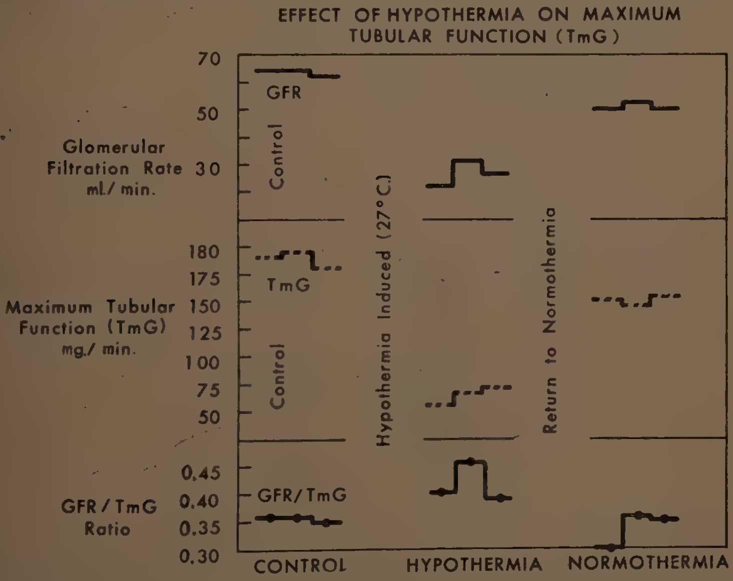

Figure 4. Hypothermia depresses maximum tubular function (TmG) as well as glomerular filtration rate.

Effect of Hypothermia on Renal Damage from Ischemia

Simultaneous occlusion of the aorta and left renal artery under normothermic conditions resulted in severe functional damage to the kidney in which the renal artery was occluded for periods of three hours (TABLE 4). The opposite kidney, although subjected to pressures below the threshold of filtration by the aortic occlusion, showed no change from control to the postocclusion observations.

Changes in urinary volume followed closely those in renal function (TABLE 4). The occluded kidney showed a marked reduction in urinary volume as compared to the control observations, whereas the opposite kidney showed no change. Often the occluded kidney was completely anuric. These findings were consistent and were significant throughout.

Levels of sodium and potassium in the plasma did not change consistently from the control to the postocclusion period, although individual dogs did show variation in levels of plasma sodium. Excretion of sodium was markedly depressed from control levels in the occluded kidney. Although this reduction in excretion of sodium was usually very marked in the damaged kidney, the latter alterations were so variable that the significance could not be demonstrated by statistical methods. In the animals in this group there was a slight increase in excretion of potassium in the unoccluded kidney, in contrast to marked reduction in the occluded kidney.

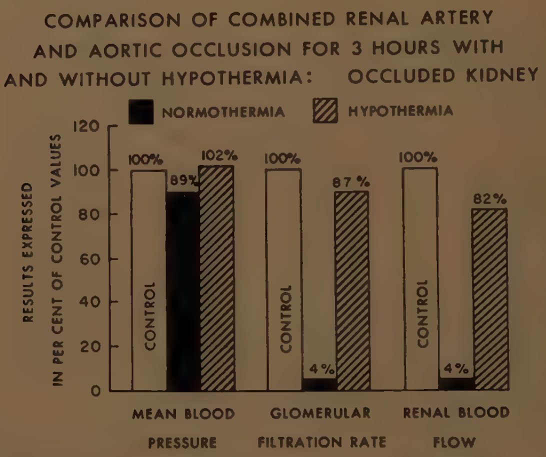

FIGURE 5. Comparison of the degree of renal damage from ischemia under normothermic and hypothermic conditions. Follow-up renal function studies were done 3 days after the control observations and the 3-hour periods of ischemia. Hypothermia had a marked protective effect against renal damage due to ischemia.

Table 4 also shows the results of combined aortic and left renal arterial occlusion for three hours under hypothermia. There was no change in the mean blood pressure from the control to the postocclusion observations. Glomerular filtration rate and renal blood flow in the unoccluded (*right*) kidney were not affected and, in fact, showed an increase in function which, however, was not significant. The glomerular filtration rate in the occluded kidney was 87 per cent of control values and the renal blood flow was 82 per cent of the control observations, which again was not significant. However, due to the slight increase in glomerular filtration rate and renal blood flow in the unoccluded kidney and the slight decrease in function on the occluded side when the two kidneys were statistically contrasted with each other, there was a significant difference ($p < 0.05$). Water and potassium excretion again were increased in both kidneys slightly over the control values but, when the observations made on the right and left kidneys were statistically compared, none of the alterations in water and electrolyte excretion were significant.

The glomerular filtration rate and renal blood flow in the occluded kidney were 4 per cent and 4 per cent of the control values, respectively, following combined aortic and renal arterial occlusion for 3 hours at normal body temperature, and 87 per cent and 82 per cent, respectively, following combined occlusion for 3 hours during hypothermia.

FIGURE 5 further compares the renal effects of occlusion with and without hypothermia. The longer the duration of occlusion, the greater the depression in renal function. This is true whether occlusion was under hypothermic or normothermic conditions. The marked quantitative difference in function between the normothermic group and the hypothermic group is obvious. Hypothermia prolongs the period during which the kidney may be made ischemic without severely depressing its function. Thus, hypothermia of 27° C. at least doubled the period for which arterial occlusion could be maintained without resulting in severe renal damage (TABLE 4).

Hypothermia itself apparently does not produce any residual damage to the kidney, since in none of the groups studied was there a significant decrease in function in the unoccluded kidney following hypothermia. Therefore, these data indicate that hypothermia lowers tissue metabolism to the point that renal ischemia, for a prolonged period, does not result in irreversible renal damage. If this concept is true in the tissue of the kidney, it should be true to a greater or lesser degree in the other tissues of the animal.

SUMMARY AND CONCLUSIONS

(1) Observations have been made on the effect of hypothermia on renal hemodynamics and on water and electrolyte excretion in dogs and man.

(2) These observations indicate that in both dogs and man hypothermia causes a reduction in renal blood flow and in glomerular filtration. These changes are not associated with a concurrent reduction in water and electrolyte excretion until the body temperature is reduced below 27° C. The failure to depress water and electrolyte excretion may be due to depression of enzymatic processes responsible for water and electrolyte reabsorption in the renal tubules.

(3) Observations are in direct contrast to the effect of reduced glomerular filtration rate under normothermic conditions when water and electrolyte excretion is markedly depressed.

(4) The effect of hypothermia on renal damage resulting from ischemia produced by unilateral renal arterial occlusion in combination with aortic occlusion has been studied in dogs, using clearance studies as an indication of the degree of renal functional impairment. The results have been compared with data obtained from a similar experiment employing normothermic conditions.

(5) Renal damage resulting from renal arterial and aortic occlusion for periods of three hours under normal body temperature was significantly reduced under hypothermic conditions.

(6) Hypothermia should offer excellent protection to the kidney when the renal circulation is occluded for variable periods of time; hence, this procedure should be a valuable adjunct to the surgeon, not only where there is questionable renal function, but also where it is desired to prevent renal damage due to ischemia.

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EFFECT OF HYPOTHERMIA AND OF COLD EXPOSURE ON ADRENAL CORTICAL AND MEDULLARY SECRETION

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The present report deals with the effect of hypothermia on adrenocorticotropic hormone (ACTH), adrenocortical, and adrenomedullary secretion in the dog and in the human, and with the effect of cold exposure on adrenal activity in the dog. Much of this work has been reported elsewhere.

Methods

The experiments carried out in our laboratory were performed on mongrel dogs weighing between 10 and 20 kg. Either intravenous sodium pentobarbital or pentothal-induced ether anesthesia was used for the hypothermia studies, most of which were performed as acute experiments.

Adrenal venous blood samples were obtained by the method of Hume and Nelson.[1] This consisted of placing a polyethylene cannula in the lateral aspect of the lumboadrenal vein and briefly occluding the adrenal vein at its junction with the vena cava. A polyethylene snare was used so that intermittent occlusion of the vein could be produced externally whenever it was desired to obtain a sample. During the periods of occlusion all of the adrenal blood flowed out of the cannula and was collected in graduated centrifuge tubes. The adrenal venous blood samples were assayed for 17-hydroxycorticosteroid content by the method of Nelson and Samuels[2] and in some experiments for epinephrine and norepinephrine content by a modification of the method of Weil-Malherbe and Bone.[3]

Arterial blood ACTH content was measured in some dogs by the method of Nelson and Hume.[4] In this technique the corticosteroidogenic capacity of the peripheral blood is tested in the hypophysectomized dog.

Three methods were used to produce hypothermia: (1) air cooling in a cold room at −10° C., (2) an external vascular shunt through 10 ft. of polyethylene tubing submersed in ice water at −4° C., and, (3) total body immersion in ice water at −4° C. The animals were cooled to 21° to 28° C. In all experiments rewarming was accomplished by total body immersion in warm water at 45° C. Body temperature was measured by a thermocouple inserted at least 4 in. into the rectum. When adrenal venous blood flow declined to a level of 0.5 cc./min., rewarming was instituted in most cases.

Some of the animals received a constant intravenous infusion of ACTH before and during the induction of hypothermia and rewarming. In some experiments the adrenal was cooled locally while the animal was maintained at a normothermic level by an arteriovenous external shunt.

Adrenal cortical function also was assessed in normothermic unanesthetized dogs exposed to cold at −10° C., −48° C., and −78° C. In these dogs the adrenal cannula was inserted under sterile conditions and the dog was allowed to recover. The animal was then exposed to cold 3 or 4 days later, when hi adrenal corticosteroid secretion had reached basal levels. Three such dog were anesthetized with sodium pentobarbital and rendered hypothermic i an ice-water bath, without the addition of any trauma.

Results and Discussion

Sections 1 through 9 below already have been published in brief by Hum Egdahl, and Nelson;[5] items 1 through 7, by Egdahl, Nelson, and Hume The results discussed under section 9 were published by Egdahl and Richards while those under section 10 were published by Egdahl, Hume, and Rich ards.[8] Those under section 11 were mentioned in another context by Hum and Bell.[9] Those discussed under section 12 were not carried out in ou laboratory, but were reported by Bernhard.[10]

(1) *Influence of hypothermia on the adrenal cortical response to trauma.*[5, 6, 11,] It was found that adrenal 17-hydroxycorticosteroid production in the traumatized animal decreased to low levels during the production of hypothermi and returned rapidly to normal upon rewarming. In FIGURE 1 it may noted that the traumatized dog secreted large amounts of corticosteroid whe its body temperature was about 37° C., but that there was a fall in secreti as the temperature went down to 21° C. When the dog was rewarmed, was noted that the corticosteroid secretion was again at a high level. In th majority of experiments the decline in corticosteroid output usually began a rectal temperature between 34° and 35° C. and continued to fall as the bod temperature fell. There was also some decrease in adrenal venous blood flo during the production of the hypothermia. This decreased flow per se can not be the explanation for the lower corticosteroid secretion because oth physiological circumstances, such as oligemic shock, produce a decrease adrenal blood flow without a decrease in corticosteroid output. Simila results were obtained by Ganong *et al.*[12]

(2) *Adrenal cortical activity when ACTH was administered during hyp thermia.*[5, 6, 11, 12] In experiments in our laboratory a continuous infusion ACTH administered to the traumatized animal before, during, and after th production of hypothermia failed to produce an increased corticostero output during hypothermia above that seen when ACTH was not admini tered.[5, 6, 11] Similar results were obtained by Ganong *et al.*,[12] who gave sma doses of ACTH when the animal was hypothermic. Thus it would appe that the adrenal cortex had become unresponsive to pituitary stimulation as consequence of the hypothermia. The response to ACTH stimulati returned rapidly when the animals were rewarmed.

(3) *Blood ACTH levels during hypothermia.*[5, 6] Although it had bee demonstrated that the adrenal cortex is relatively unresponsive to ACT during hypothermia, the possibility still existed that pituitary ACTH secr tion also might be reduced during hypothermia. Accordingly, this wa tested for in several animals by the measurement of peripheral blood ACT levels following trauma before the induction of hypothermia, during th induction of hypothermia, and after rewarming. It was found that bloo ACTH levels, which were high as a consequence of the trauma, fell to leve

oo low to measure by the techniques used, during hypothermia, and again ose to measurable levels during the period of rewarming.[5, 6] It thus would ppear that both pituitary and adrenal cortical activity were reduced by the ypothermia (FIGURE 2).

(4) *Effect of various methods of producing hypothermia.* These effects of ypothermia were noted whether the animal had been cooled by being placed in a cold room, by submersion in an ice-water bath, or by the cooling of an extracorporal arteriovenous shunt. Furthermore, the same effects were noted whether ether anesthesia or nembutal anesthesia was used.[5, 6]

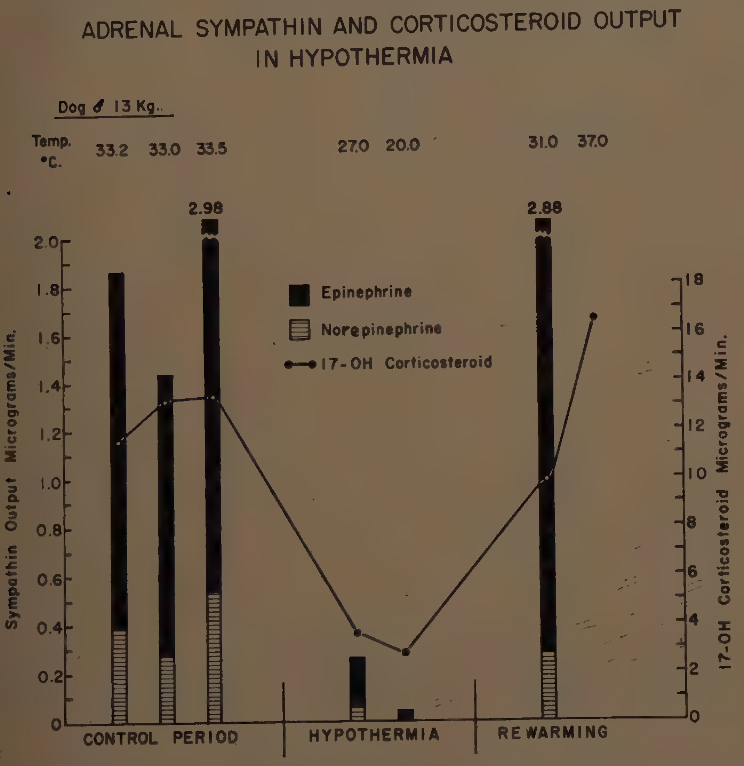

FIGURE 1. The blood ACTH levels and adrenal vein blood 17-hydroxycorticosteroid output in a dog traumatized under ether anesthesia and then subjected to hypothermia. It may be seen that there is a marked depression of corticosteroid secretion during hypothermia, but an increase again after rewarming. Blood ACTH, which is at a measurable level before the induction of hypothermia, becomes too low to measure during hypothermia. On rewarming, ACTH is again present in easily detectable amounts. Reproduced by permission from *National Academy of Sciences—National Research Council Publication.*

(5) *Maintenance of normal blood pressure during hypothermia.*[5, 6, 11] To rule out the possibility that the fall in blood pressure observed with hypothermia was the cause of the reduced secretion of corticosteroids, the blood pressure was maintained at normal levels in 2 animals undergoing hypo-

thermia. These animals were given infusions of norepinephrine, which made it possible to produce hypothermia without the fall in blood pressure usually seen. In spite of the fact that the blood pressure was maintained, the usual pattern of decreased adrenal cortical steroid output followed upon the induction of hypothermia. It was noted, furthermore, that marked cardiac irregularities occurred as a consequence of the combination of norepinephrine administration and the production of hypothermia. This suggested that the depressed adrenal secretion was not a consequence of changes in blood pressure.

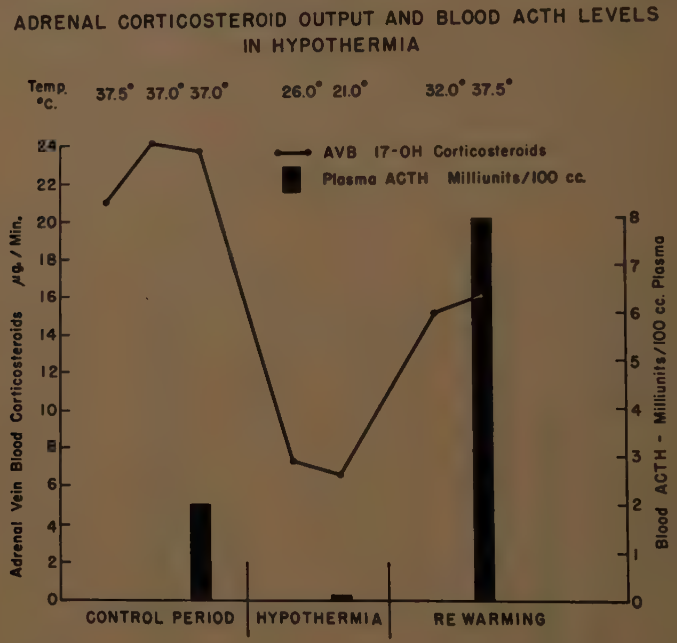

FIGURE 2. Epinephrine, norepinephrine, and corticoid secretion in the adrenal venous blood of a dog traumatized under ether anesthesia before, during, and after induction of hypothermia. A marked decrease in epinephrine and norepinephrine output occurs during hypothermia. Reproduced by permission from *National Academy of Sciences—National Research Council Publication.*

(6) *Effect of cold applied locally to the adrenal.* In three experiments the adrenal itself was cooled while the remainder of the animal's body was maintained at normal temperature by an extracorporal shunt that was immersed in a warm-water bath. There was a significant fall in adrenal corticosteroid secretion in spite of the maintenance of normal temperature in the rest of the body.[5, 6] This suggested that the effect of cold was a direct one on the adrenal rather than a secondary manifestation of the generalized hypothermia. It is likely that the cold produces changes in the adrenal enzyme systems which reduce the effectiveness of the adrenal in carrying out corticosteroidogenesis.

(7) *Production of hypothermia in the nontraumatized animal under anesthesia.*[5, 6] In three dogs in whom adrenal cannulation had been carried out previously, anesthesia was induced with intravenous sodium pentobarbital. The adrenal corticosteroid secretion was at a low ebb because the animal had not been traumatized recently. Hypothermia was induced by ice-water immersion, and it was noted that there was no increased adrenal corticosteroid secretion as a consequence of the production of hypothermia. It appears, therefore, that the production of hypothermia is not a stimulant to pituitary adrenal cortical activity in the dog.[5, 6]

(8) *Secretion of epinephrine and norepinephrine by the adrenal medulla during hypothermia.*[5] It was found that when the dog was traumatized under ether anesthesia a marked increase in adrenal medullary secretion of epinephrine and norepinephrine was seen.[13] When hypothermia was induced, there was a striking fall in epinephrine and norepinephrine secretion in the adrenal venous blood, and the secretion of these substances rapidly rose to high levels upon rewarming the animal[5] (FIGURE 1). It would appear, therefore, that hypothermia depressed not only the adrenal cortical function, but also adrenal medullary function. This depression of the adrenal medulla is probably fortunate because of the previously mentioned tendency toward cardiac irregularity when high circulating levels of norepinephrine are seen in combination with hypothermia.

(9) *Effect of a cold environment upon adrenal secretion in the resting, unanesthetized dog.*[5, 7, 14] Although it has been reported by Selye and Schenker[15] that exposure to a cold environment is a definite stress to the adrenalectomized rat, it was found that in the dog exposure to −10° C. did not produce a significant increase in adrenal corticosteroid secretion.[14] When the animals were exposed to temperatures of −48° to −78° C., it was found that a marked increase in adrenal corticosteroid output occurred soon after the onset of exposure.[7] In 9 of the 10 animals tested this response persisted for from 1 to 3 hours, after which adrenal corticosteroid secretion returned to the low pre-exposure levels despite the continued exposure to the cold. The intravenous administration of 40 U. of ACTH produced a rapid increase in adrenal corticosteroid secretion, even when the animals had been in the cold for several hours. Healthy dogs exposed to temperatures of −47° C. for 28 hours and −79° C. for 5 hours did not become hypothermic. It may be concluded, therefore, that the exposure of normal dogs to temperatures of −10° C. did not produce hypothermia or adrenal cortical activation and did not alter adrenal responsiveness to ACTH. Exposure of dogs to temperatures of −48° C. or −78° C. produced temporary adrenal activation, but did not produce hypothermia, prolonged adrenal activation, or alterations in adrenal responsiveness to ACTH.

(10) *Tolerance of the dog to cold.*[8] In one set of experiments 17 healthy dogs that had previously recovered from operations in which adrenal cannulas were inserted were exposed to temperatures ranging from −5° to −79° C. Only one of the animals in this series became hypothermic, the temperature remaining within the normal range in all other animals. Two animals were exposed to temperatures of −32° C. for 4 to 5 hours without any ill effects

or change in temperature. Ten dogs were exposed to temperatures of −46° to −50° C. for 4 to 27 hours without ill effects or the development of hypothermia. Of seven animals exposed to temperatures of −75° to −79° C. for periods ranging from 3 to 5 hours, one of the group became hypothermic, as previously stated. Two bilaterally adrenalectomized dogs were subjected to temperatures of −46° to −56° C. for a period of 4½ hours. An additional adrenalectomized dog was subjected to temperature of −5° C. on two occasions, once for 4 hours and once for 8 hours. Hormone therapy had been withdrawn from these animals for as much as 5 days prior to the exposure period. None of the 3 dogs suffered any ill effects. Two other adrenalectomized animals, not previously reported, were subjected to temperatures of 0° C. for a period of 8 hours after all supportive therapy, which had consisted only of DCA, had been withdrawn for 3 days prior to the exposure. They suffered no apparent ill effects from the exposure, and showed no significant change in their body temperature. It would appear, therefore, that dogs are able to withstand very low temperatures without changes in body temperature or other ill effects. It would appear further that the presence of the adrenal cortex is not necessary for this resistance to extreme cold, at least under the conditions of these experiments. Giaja and his associates[16, 17] have studied the level of cold exposure that produces hypothermia in various animals and birds. They found that −160° C. was necessary to make dogs hypothermic after 1 hour of exposure and that there was a different critical temperature for different species of animals and birds. Corresponding temperatures for other animals, for example, included −15° C. for the guinea pig, −25° C. for the rat, −53° C. for chickens, and −85° C. for the pigeon. Irving and Krog[18] found that the Arctic fox maintains body temperature after a 1-hour exposure to −80° C. It is apparent from these studies that the effects of cold must be individualized for the species under study and that generalizations about cold exposure to cover all species are unwarranted. It should be further noted that not only is there variation in the inherent ability of different animals to tolerate cold exposure, but that an individual tolerance to cold exposure may be created by previous exposure to a cold environment. Scholander and his colleagues[19] found that gulls could tolerate −50° C. without difficulty under ordinary circumstances but that, if they were kept inside at 20° C. for as short a period as 2 days, their feet froze rapidly when they were returned to a −20° C. environmental temperature. It was somewhat surprising that the adrenalectomized dog was able to withstand severe cold without apparent difficulty, and one might be tempted to postulate that the animals had not been totally adrenalectomized. That such was not the case was demonstrated in all instances by withdrawing therapy several weeks after the cold experiments were carried out, and noting that all animals died of adrenal insufficiency within a period of 10 days. No remaining adrenal tissue was found at autopsy.

Smith[20] has reviewed the pertinent literature on the resistance of animals to cooling and freezing.

(11) *Effect of hypothermia to 30° C. on adrenal secretion in the human.*[9] A study was carried out by Hume and Bell[9] in which measurements of adrenal

venous blood secretion of corticosteroid, epinephrine, and norepinephrine were made in human patients undergoing surgical operations. The minute output of these substances was established in 9 patients who were operated upon under pentothal-nitrous oxide-Demerol-curare anesthesia. The range of adrenal cortical and medullary secretion in these patients is shown in FIGURE 3. Similar measurements were made in one patient who was operated upon under hypothermia, and it was found that under these circumstances adrenal secretion of corticosteroids was lower than that seen in any of the control patients. The secretion of epinephrine and norepinephrine was within the range seen for the other patients. These data, while very scant, are similar to the results obtained in the dogs, and would suggest that there is a reduced adrenal cortical secretion evident at 30° C. in the human while, at this temperature, no decline is yet seen in the secretion of epinephrine and norepinephrine. It is likely, on the basis of the experiments on dogs, that

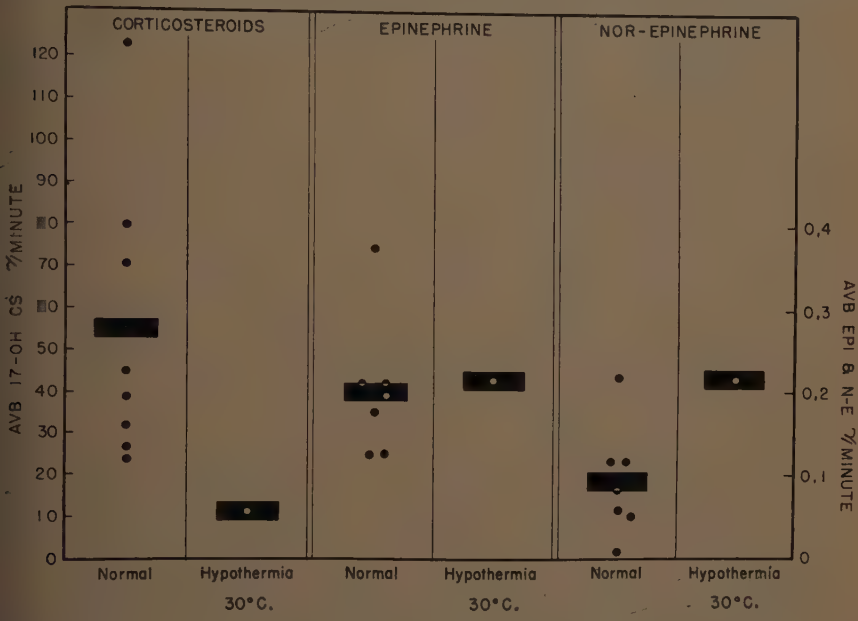

FIGURE 3. Adrenal venous blood corticosteroid, epinephrine, and norepinephrine output in the human. The circles represent an average of the values obtained in a single patient during the period of the test. The horizontal bars represent the average of all of the patients in the series. The adrenal venous blood corticosteroid, epinephrine, and norepinephrine production expressed in micrograms per minute in eight normothermic patients undergoing operative trauma is compared with that seen in a single patient undergoing a similar or greater degree of trauma under hypothermia at 30° C. The anesthesia in all cases was pentothal-nitrous oxide-Demerol-curare. It may be seen that corticosteroid production was decreased markedly in the hypothermic patient below that seen for any of the patients in the normothermic group. The production of epinephrine and norepinephrine was not significantly different under hypothermia from that seen in normothermic patients.

an increasing depression of both adrenal cortical and medullary secretion would have been noted had the temperature been carried lower. Since this is the range ordinarily utilized in clinical hypothermia, however, it would appear that a maximal depression of adrenal secretion is not seen under these circumstances.

(12) *Effect of hypothermia on peripheral corticosteroid levels in the dog and man.*[10] Bernhard[10] reported that the production of hypothermia in the traumatized dog is not accompanied by decreases in peripheral blood levels of free 17-hydroxycorticosteroids. He concluded that this is due to the fact that there is a depression of the liver's ability to conjugate corticosteroids which is equal to or greater than the depression of adrenal production of these substances. As a consequence of this there is a piling up of adrenal corticosteroids in the peripheral blood. The temperature of his animals was 25° C. Peripheral samples were obtained also in a small group of patients undergoing surgery with hypothermia. In the patients, of course, the hypothermia was induced after the start of anesthesia, but before any trauma had been applied to the patient. There was no increase in peripheral corticosteroid level as a consequence of the induction of hypothermia, nor was there any rise in the peripheral corticosteroid level as a consequence of the operation during the time that the patient was hypothermic. When the patient was rewarmed there was a marked rise in peripheral corticosteroid levels. It was concluded that the ability of the liver to conjugate corticosteroids during hypothermia was depressed, that the immersion cooling did not produce a rise in corticosteroid levels, that peripheral corticosteroid levels already elevated before the induction of hypothermia remained elevated, and that when hypothermia was induced before operative trauma was begun the operation failed to produce a rise in peripheral corticosteroid levels.

It was reported by Georges and Cahn[21] that the pituitary failed to release ACTH in hypothermic states below 27° C. and that it was necessary to administer exogenous ACTH to achieve an adrenal cortical response. These experiments were performed using adrenal ascorbic acid depletion as a measure of ACTH release. The authors found that there was an adrenal ascorbic acid depletion in rats cooled as low as 22.5° C. and given exogenous ACTH. Khalil[22] also discovered that no adrenal ascorbic acid depletion occurred in rats cooled to 20° C. unless exogenous ACTH was administered. He concluded that the anterior pituitary did not release ACTH in hypothermia. In both of these studies the administration of ACTH to rats that were hypothermic with temperatures from 20° to 22.5° C. resulted in adrenal ascorbic acid depletion. It is difficult to assess these results because they are based on indirect methods for measuring adrenal cortical secretion. When the corticosteroids are measured directly in the adrenal venous blood in the dog, it has been found, as outlined above, that adrenal responsiveness is essentially absent at temperatures below 23° C.

It is worth noting that the adrenal cortex and medulla are not damaged by hypothermia and are immediately responsive to stimulation when the animal is rewarmed.

In a few experiments adrenalectomized dogs were given infusions of hydrocortisone under anesthesia in the normothermic and hypothermic states. There was a very distinctly slower rate of disappearance of the injected hydrocortisone during hypothermia.[6] This may explain the results obtained by Bernhard[10] in which peripheral corticosteroid levels did not fall in hypothermia.

Conclusions

(1) Trauma under ether anesthesia produces a marked increase in pituitary ACTH and adrenal cortical secretion. Induction of hypothermia greatly depresses the output of these hormones. Prehypothermic ACTH and corticosteroid levels are again noted when the animal is rewarmed.

(2) Adrenal sensitivity to exogenous ACTH administration is reduced markedly under hypothermia.

(3) Cooling of the adrenal with maintenance of normal body temperature is accompanied by a marked depression in adrenal responsiveness to ACTH.

(4) Adrenal medullary secretion of epinephrine and norepinephrine is sharply reduced in hypothermia.

(5) Induction of hypothermia per se under anesthesia, but in the absence of trauma, does not act at any time as a stimulant to the pituitary-adrenal cortical secretion.

(6) Cold exposure without the development of hypothermia does not alter adrenal responsiveness to ACTH. Exposure to −10° C. provides almost no stimulus to pituitary adrenocortical secretion in the dog, while exposure to −48° and −78° C. is followed by only a transient increase in pituitary-adrenocortical activity.

(7) The dog can tolerate extremely low temperatures without change in body temperature. The adrenal cortex is not necessary for this tolerance.

(8) There is a decreased metabolism of corticosteroids in the hypothermic adrenalectomized animal.

(9) The production of hypothermia at 30° C. in a single clinical case demonstrated that there was a definite reduction in adrenal corticosteroid secretion in the human under these circumstances. At this temperature there was no significant difference from the normal patients in the adrenal secretion of epinephrine and norepinephrine.

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HYPOTHERMIA AND ITS EFFECTS ON THE SENSORY AND PERIPHERAL MOTOR SYSTEMS

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Hypothermia can be defined as a lowering of the body temperature of a homoiothermic animal, and again this may be in whole or in part. Thus it is emphasized that, historically, the first use of the effects of hypothermia on the nervous system was a utilization of the fact that cooling blocks activity in sensory conducting systems. The first records of this have been lost in antiquity. According to data available to me,[1] the earliest record of the use of snow and ice water as a local analgesic was that of Ibn Sina in the Eleventh Century. Later, Severinus[2] reported the use of snow and ice, but it probably was not noted again until the time of Napoleon, when the latter's military surgeon Baron Larrey observed the effect of snow and ice on his treatment of surgical traumatic wounds. Many others[2] made similar observations. These investigators considered cold superior to various morphine derivatives and other narcotic agents.

Remarkably few data are available on the fundamental thermodynamic aspects of the functioning of conductile tissue, even though it was the effects of temperature change on the membrane potential of muscle that led Bernstein[3] in 1902 to formulate his concentration cell hypothesis of the membrane that has remained so significant (if now perhaps only heuristically so) down through the years.

Previously Hermann[4] had shown that a cooled locus on a muscle becomes relatively electronegative; Cruetzner[5] and, later, Verzar[6] and Bremer and Titeca,[7] showed the same effect for peripheral nerve.

In 1946, Bernhard and Granit[8] found that impulses were generated when a nerve was locally heated or cooled from 37° C. Later, Euler[9] and Granit and Lundberg[10] showed that it was the large myelinated fibers of mammalian nerve that were selectively fired by cooling, an effect produced by a generated potential created by the relative depolarization of the locally cooled membrane. Lundberg[11] studied A (cat) and C fibers (cow splenic nerve), and found that the membrane potential of the former had a maximum (that is, was at thermal equilibrium) at 37° C. while that of the latter was at 25° C. This, then, is the reason that local cooling fires only large fibers.

The effects of cooling on the *action* potential depend greatly on the species and previous history of the animal. Lucas[12] found that the conduction velocity of frog nerve decreased with a fall in temperature. In general, the amplitude of the spike goes through a maximum which occurs at a lower temperature in cold-adapted (winter) frogs,[7, 13, 14] in animals capable of hibernation,[15] and in cold-adapted birds (Herring gull).[16] Adrian[17] found that the duration of the absolutely refractory period and the electric response of cooled nerve varies with temperature ($Q_{10} = 3$). Lorente de Nó[18] found in frog nerve that the changes in the action potential brought about by cooling were identical to those produced by anoxia or depolarizing agents, although the block that eventually occurs is not due to depolarization. In the mammal Lundberg[11] found that A-fiber spikes were maximal at about 30° C.; C-fiber spikes, at about 5° C. There were similar differences in the maxima of the negative after-potential in the two groups of fibers. Tasaki and Spyropoulos[19] most recently have studied the effects of cooling on isolated frog toad, and squid giant axons.

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* Deceased.

Actual block of conduction by cooling is, as has been said, an old observation. Again, the species of animal and its history are critical. Cooling blocks mammalian nerves at higher temperatures than frog nerves, as has been shown by many investigators.[20-23] Tropic or summer frogs block at a higher temperature than their winterized brethren.[24, 25] This is true also of the Herring gull, as Chatfield *et al.*[16] showed.

Dog sciatic motor fibers[5] block at 6° C., sensory ones at 1° C. The dog vagus[20, 24] blocks at 0° C., but the rabbit vagus ceases functioning at 15° C Some of the variability of these results may be due to differences in the distance of nerves cooled in any given experiment.

Sciatic and phrenic nerves from mammals capable of hibernation are no blocked by cooling, which would prevent conduction in nonhibernating animals,[15, 26] whereas a neural adaptation to cold can be produced by varying the nerves' environmental temperature in the gull;[16] this is not true in the rat.[15]

All the differences between nerves may be related to variability in their internal ionic constitutions. Lundberg[11] has shown the role of K^+ in altering the thermal properties of mammalian fibers.

The only data available to me on the effects of temperature on sensory receptor organs have been well reviewed by Zotterman[27] on the effects o temperature on the discharge from tongue receptors. The physiology is so complicated that I shall only mention the existence of this excellent work.

In conclusion, I offer some brief remarks on the effects of cooling on the more peripheral neuromuscular junctions, although the neuromuscular junction is commonly regarded as an example of synaptic systems, and the effects of temperature on other such systems have been studied.[28-30] Several years ago, Alex Doudoumopoulos and I, finding no data on the effects of cooling on neuromuscular function, began an investigation which we have continued. Since then Choh-Luh Li has published his results on the effect of cooling on neuromuscular transmission in the rat as investigated with micromethods.[3 He finds that neuromuscular transmission is blocked in this animal at 5° C. This effect was preceded by changes in the spike potentials recorded from the end-plate region when the animal's temperature had been lowered to only 15° C.

In my work I used the rat sciatic-gastrocnemius preparation, recording muscle tension isometrically and stimulating the nerve supramaximally while changing muscle temperature locally. The results can be summarized as follows:

General cooling had only slight effect on the tension developed in the twitch responses to single sciatic shocks, tension being greatest at intermittent temperatures (18 to 26° C.). Twitch duration was prolonged at lower temperatures.

The effects of temperature became more marked when tetanic stimuli were delivered. In the lower frequency ranges, cooling the muscle caused an increase in tension that appeared to be correlated with the fact that at low temperatures there was a greater fusion of contractions.

The relationship between the variables of tension, frequency, and temperature was a complex one. At stimulus frequencies of 3 to 15/sec., muscle functioned better (that is, developed more tension) as it was progressively cooled. At all frequencies used, it functioned better at 26.5° C. than at 37° C., and even better at 18° C. if stimulus frequency was under 40. At no frequency was a normal physiological temperature the optimal one for functioning of muscles.

However, perhaps surprisingly, these results from indirect stimulation were duplicated after the same animal was curarized and the muscle stimulated directly. Hence, while hypothermia may indeed have some effects on the neuromuscular junction, these are overshadowed by direct effects on the contractile mechanism itself.

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HYPOTHERMIA AND REACTION PATTERNS OF THE NERVOUS SYSTEM*

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Cooling of the central nervous system results in a variety of functional changes indicating that both the activity of individual structural elements and the patterns of reactions of the system have changed. Normally, impulses originating from sensory receptors enter the spinal cord by way of specific fibers of certain dorsal roots. These orthodromic impulses are normally of brief duration and confined to very precise channels such as the lower segmental reflex paths. The incoming volley also ascends the cord in specific pathways to initiate or modify activity in higher centers. These, in turn, exert certain integrative influences that confine and refine the segmental response while, at the same time, evoking an arousal reaction or some other appropriate general body response. These sensory stimuli initiate in the cerebral and cerebellar cortex momentary localized potentials described as evoked potentials indicative of an anatomical and functional organization of these higher regions.

Cooling is generally considered to have a depressant action, but it has long been known that there is a phase of hyperresponsiveness (Barron and Matthews, 1938*b*; Grundfest, 1941) and hyperreflexia (Fay and Smith, 1941) that precedes a stage of general depression. During this phase of hyperresponsiveness incoming volleys evoke an antidromic discharge over dorsal roots and afferent nerves momentarily capable of interfering with incoming stimuli (Barron and Matthews, 1938*a*; Brooks and Koizumi, 1956). Single stimuli that normally evoke single responses in motoneurons cause repetitive discharges, and at certain temperatures a tetanic discharge appears in both dorsal and ventral roots. This seemingly is of spontaneous origin (Ozorio de Almeida, 1943; Koizumi, 1955). Furthermore, a volley coming in from a muscle afferent evokes a polysynaptic rather than monosynaptic response and a reflex discharge that is no longer confined to the motoneurons of a few cord segments. There is a much greater spread of the excitation and a much more diffuse response (Brooks *et al.*, 1955). Segmental facilitation, inhibition, and posttetanic potentiation are prolonged (Koizumi *et al.*, 1954) and the reticular system is reported to be hyperactive at temperatures of approximately 28° to 27° C. (Ogata *et al.*, 1958).

In order to show examples of changes in responses of the nervous system during hypothermia and to give some explanation of their cause, an initial illustration is provided by FIGURE 1 that shows the simultaneous augmentation in amplitude and duration of a spinal reflex and cerebral cortical-evoked potentials that occur as a result of cooling of the central nervous system.

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Cerebellar-evoked potentials are similarly affected. Analysis of the electroencephalogram during the phase of hyperresponsiveness shows an increase in amplitude of deflections without change in frequency (Suda *et al.*, 1957). It already has been stated that in hypothermia, motor fiber discharge from ventral roots is augmented, repetitive and, at times, seemingly spontaneous. This hyperactivity apparently is not confined to the large motor fibers innervating skeletal muscle. FIGURE 2 shows a spontaneous discharge that appears to be from the small efferent fibers. The rate of firing of these elements increases in hypothermia, as is shown in the illustration. A similar spontaneous discharge occurs in the autonomic efferents (Suda *et al.*, 1957). Normally, a myotatic reflex is unassociated with discharge in the hypogastric nerve, but in hypothermia there is a spill-over into this autonomic outflow. Involvement of the hypogastric nerve in what normally would be a simple monosynaptic reflex evoked by stimulation of large-diameter muscle afferent fibers certainly indicates a break down of normal patterns of response in hypothermia.

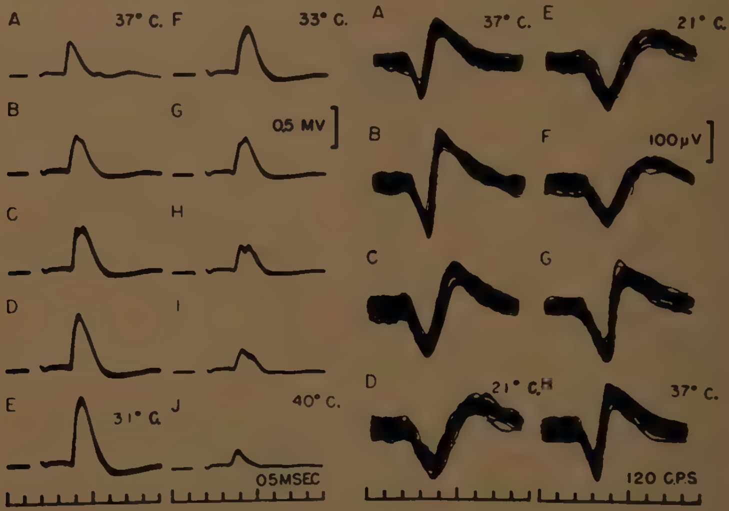

FIGURE 1. The effect of cooling on the monosynaptic reflex (*left*) elicited by gastrocnemius nerve stimulation and on cerebral cortical potentials (*right*) evoked by stimulation of the contralateral superficial radial nerve. All records shown are comprised of sixty superimposed consecutive potentials.

It should perhaps be pointed out before proceeding to an explanation that this hyperresponsiveness just described is not due to hyperexcitability. Thresholds of axons and central neurons to direct electric stimulation are raised (Brooks *et al.*, 1955). There is no change in resting potential of the neurons and no indication of membrane instability. Slowed recovery after stimulation in hypothermia is indicated by prolongation of action potentials as well as by other signs (Tasaki, 1949).

In turning now to a search for explanations, it is proper to recall that the effectiveness of a stimulus is determined by its duration as well as its amplitude. When one records afferent volleys entering the progressively cooled cord from simultaneously cooled dorsal roots, an increase in area of the action potential is seen. The increase in duration can be ascribed to lengthening of individual fiber action potentials and an augmented disparity of conduction speeds due to greater susceptibility of some fibers to cooling depression. This prolongation of the action potential is much greater than the reduction in amplitude. The afferent signal thus initially increases in potency in hypothermia.

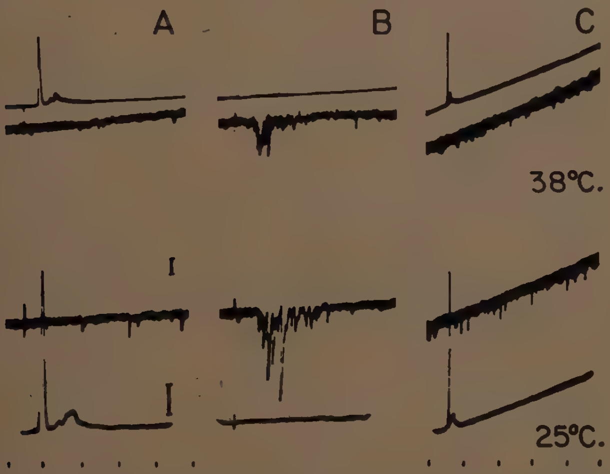

FIGURE 2. Reflex response recorded from L_7 ventral root of left side (*lighter tracing*) and recordings from a branch of tenuissimus nerve of the right side (*heavy tracings*). In *A* and *C* the left gastrocnemius nerve was stimulated (see artifact) and, in *B*, the right L_7 dorsal root was stimulated. Note greater activity in tenuissimus nerve at lower temperature. Time marks: 10 msec. for *A* and *B* and 50 msec. for *C*. Amplification marker is 0.5 mv. for root and 0.1 mv. for nerve recording.

This same prolongation of action potentials has been observed to occur in elements within the cord, such as the fibers and the interneurons that constitute the intraspinal components of the reflex pathways. Presynaptic changes are thus of greater magnitude and seem to be capable of exciting a greater than normal number of postsynaptic elements. Suda *et al.* (1957) found by intracellular recording that the action potentials of cooled motoneurons were prolonged, but not increased in amplitude. The increase in amplitude of the ventral root action potentials in hypothermia, therefore, must be due to excitation of a higher percentage of the elements of the motoneuron pool. In FIGURES 3, 4, and 5, recordings of reflex responses and action potentials from a single motoneuron are shown. Three afferent nerves were stimulated repeatedly in sequence while the cord was being cooled. The points illustrated by records such as these shown here are the following:

(1) Cooling increased reflex action, enabling a nerve that normally evoked

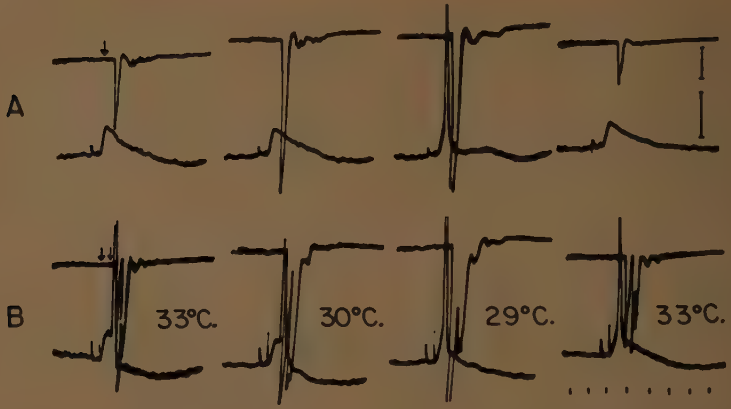

FIGURE 3. *Upper tracings* are from L$_7$ ventral root, and *lower tracings* are recordings from a single motoneuron. Activity was induced by stimulation of gastrocnemius muscle afferents. Negativity was recorded downward on both beams in this and subsequent figures. Beams are not exactly synchronized; arrows indicate time of stimulation and time lag of upper beam. Single stimuli were used in *A*; in *B*, pairs of stimuli were employed. Note that conditioning stimulus alone was effective at 29° C.; 5 msec. time marks. Amplification markers: top beam, 0.2 mv.; bottom, 20 mv.

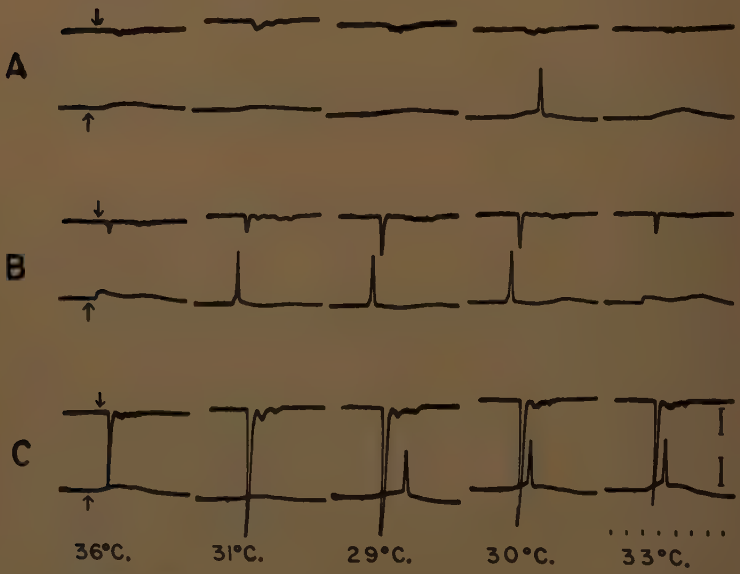

FIGURE 4. Recordings from L$_7$ ventral root (*upper tracings of pairs*) and motoneuron Arrows indicate stimulus artifacts and beam synchronization. Stimulation of sural nerv (*A*), gastrocnemius (*B*), tibialis posterior (*C*). Time: 5 msec.; amplification: *top*, 0.2 mv. *bottom*, 50 mv.

little activity along the reflex path under study to initiate a response of significant magnitude as though a new reflex connection had been established. (2) Latency of motoneuron discharge was decreased; this could be explained on the basis of a more effective synaptic excitatory action. (3) More motoneurons were recruited as cooling occurs. It can be seen that at normal temperature the motoneuron from which the recording was taken was not involved in the reflex responses evoked by two of the three afferents stimulated. This constitutes evidence of a loss of specificity in reflex reactions.

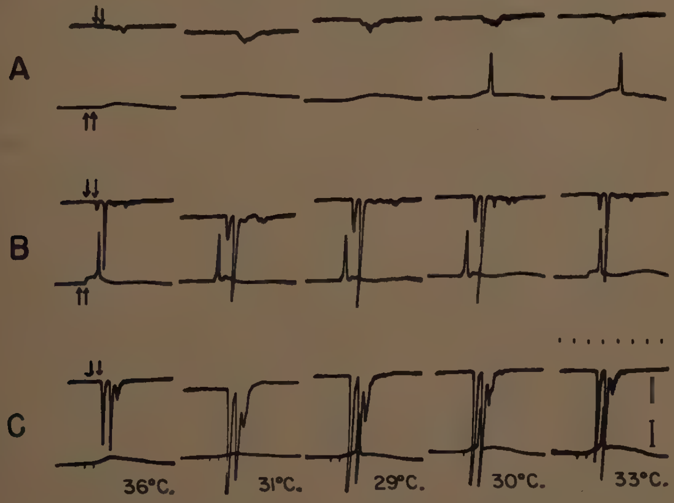

FIGURE 5. Same as FIGURE 4, except that double stimuli are used.

Two other matters are of importance in explaining these observed phenomena. It has been stated that the power of accommodation is impaired in hypothermia (Schoepfle and Erlanger, 1941). This change theoretically might cause fibers to be more responsive to field effects and to discharge repetitively when acted upon by long-continued excitatory processes. At each synaptic junction there is thus the possibility of a step-up effect in a reflex arc and involvement of a greater than normal number of postsynaptic elements. It has been suggested (Lloyd and McIntyre, 1949) that fiber interaction or field effect evokes the dorsal root reflex that is so much augmented in hypothermia that it occurs even in association with a monosynaptic reflex (Brooks and Koizumi, 1956). It is also possible that appearance of the dorsal root reflex is associated with augmented activation of interneurons in hypothermia.

Evidence of a direct effect of hypothermia on activation and reactions of interneurons is available. FIGURE 6, which shows a recording from a single interneuron, demonstrates the increase in repetitive firing that occurs in such elements as cord temperature is reduced. This augmentation of repetitive response provides another amplifying action that conceivably is responsible in part for involvement of a higher percentage of motoneurons in hypothermic than in normothermic reflexes. It should be pointed out here that cooling does not in all cases augment repetitive firing of interneurons. At least a few interneurons showed a block or a decrease of their repetitive response as the cord was cooled (FIGURE 7). These differences may be due to a greater susceptibility to cold or to a more fundamental difference in property and functional role.

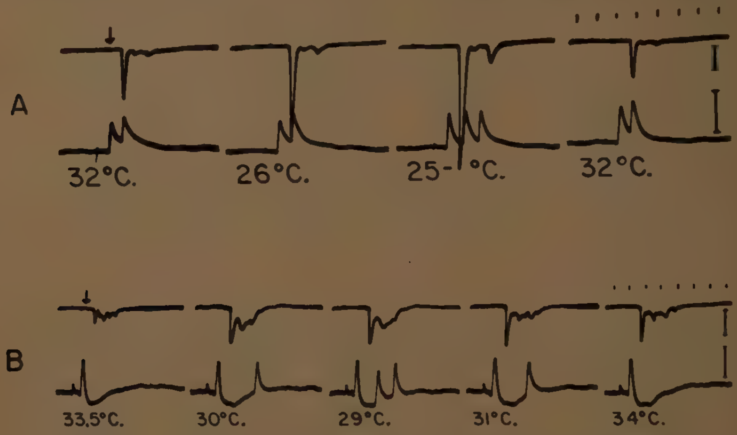

FIGURE 6. Reflex response in L₇ ventral root (*upper tracing*) and response of an interneuron (*lower tracing*). Activity evoked by stimulation of tibialis posterior in both *A* and *B*. Time: 5 msec.; amplification in *A* is 0.5 mv. (*upper*) and 5.0 mv. (*lower*); in *B*, 0.2 mv. (*upper*) and 2.0 mv. (*lower*).

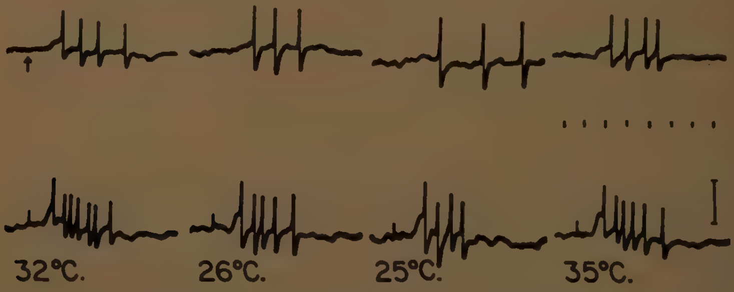

FIGURE 7. Individual interneuron discharge induced by stimulation of sural nerve (*top tracing*) and of tibialis posterior (*lower tracings*). Time, 5 msec.; amplification, 2 mv.

Additional evidence of a greater degree of interneuron participation in central nervous system response is provided by the change of the monosynaptic to a polysynaptic reflex as hypothermia develops (FIGURE 8). This change in the response to muscle stretch or stimulation of large-diameter muscle afferents as the cord is cooled may be due to activation of normally ineffective synaptic connections between fibers of the monosynaptic pathway and the interneurons.

It is conceivable that hyperresponsiveness, the longer duration of facilitatory and inhibitory actions, might be due to a higher level of background activity in the cord during hypothermia. Examination of this point thus far has yielded only negative evidence. Recordings from spontaneously firing interneurons have shown either no change in rate on cooling or a reduction in frequency of discharge (FIGURE 9). It can be seen also that, when inhibition of their activity occurred following initiation of a reflex, it lasted longer during hypothermia.

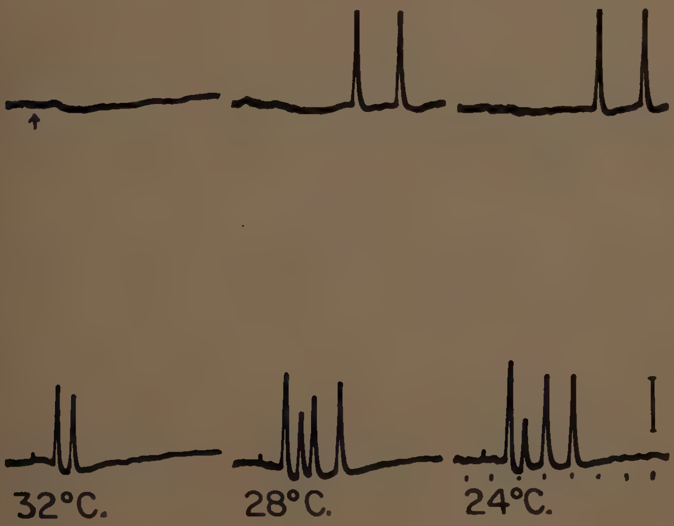

FIGURE 8. Individual interneuron activity evoked by stimulation of gastrocnemius (*top*) and tibialis posterior (*bottom tracings*). Time, 5 msec.; amplification, 2 mv.

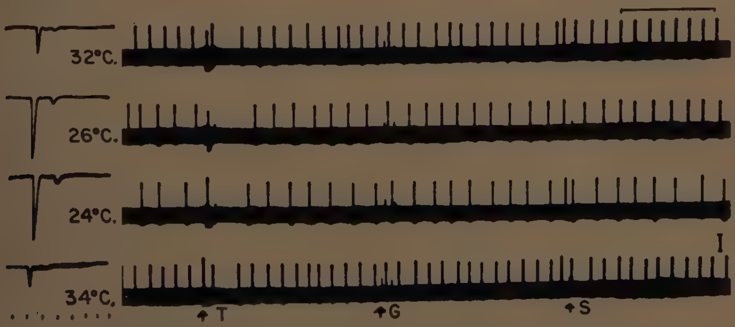

FIGURE 9. Reflex in L_7 ventral root at left. Recording of spontaneous activity in an individual interneuron at right. Time: 5-msec. time intervals for reflex and a 500-msec. time interval shown for interneuron record. Amplification: 2 mv. Stimulation of tibialis (*T*), gastrocnemius (*G*), and sural (*S*) nerves.

Below certain temperatures there is general depression of all nervous system functions, as might be expected, and reaction pathways eventually fail in a progressive fashion. A phase of hyperresponsiveness does occur and it appears that the overaction is not due to an increase in excitability, but is due to (1) repetitive discharge, probably contributed to by failure of accommodation and prolongation of excitatory potentials; (2) the greater participation of interneurons in reflex action; and (3) a greater power of recruitment at synaptic junctions because of the changes just mentioned. These same occurrences probably account also for the greater spread of activation, overflow of excitation into systems not normally invaded, and general failure of confinement of activity to normal pathways. This, of course, changes the reaction patterns of the nervous system in hypothermia.

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NEUROLOGICALLY INDUCED PHYSIOLOGICAL RESISTANCE TO HYPOTHERMIA

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Determining an Animal's Physiological Resistance to Cold

I feel that the homothermisity of animals can be characterized best with respect to cold by determining the animal's ability to prevent a lowering of its core temperature in the presence of standardized cooling loads. Cooling load-test situations utilized for this purpose are a still air temperature of −20° C. and a 3° C. air temperature with some air movement.

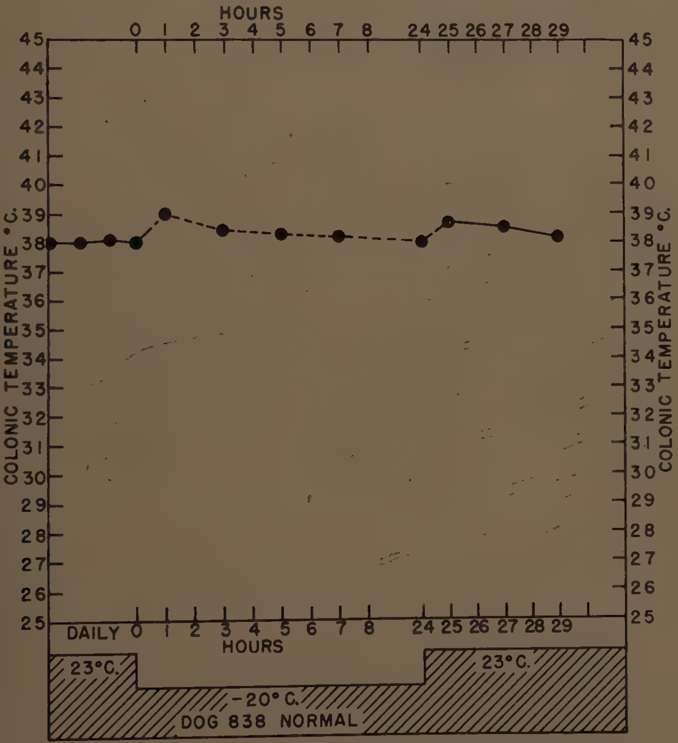

FIGURE 1. Deep colonic temperature curve for an unoperated dog before, during, and after exposure to a −20° C. air temperature for 24 hours. The broken line in the temperature curve denotes the presence of shivering.

A core temperature response to the −20° C. test situation is illustrated in FIGURE 1. As indicated at the bottom of the chart, previous to the test the animal was housed in a 24° C. air temperature. It was abruptly transferred to a cage located in a room maintained at −20° C. At the end of the exposure it was returned with equal abruptness to its original cage. An unoperated healthy mongrel dog was the subject and the core temperature observed was deep colonic. It is to be noted that by the end of the first hour core temperature had risen from 38° to 39° C. Shivering, as indicated by a broken line in the temperature curve, began some time during the first hour and was prominent at the time the first hourly temperature was taken. Subsequently, body temperature returned toward, but did not reach, the preexposure level.

This response is representative for the mongrel dog. It should be appreciated that minor variabilities in responses are frequent, but the end result, which is reliably predictable, is that a frank hypothermia never develops.

Previous to the test the animal had been fully accustomed to routine laboratory procedures, but had not been conditioned to cold. During the animal's sojourn in the cold (1) it was not restrained except for the short periods when temperature was taken and blood was drawn, and (2) it did not have benefit of food in its digestive tract. Water was continually available (when exposure is extended beyond twenty-four hours, the animal is returned to its daily feeding regime at the beginning of the second day of exposure).

In such test situations the entire animal is exposed to the cooling load and core temperature is the end point resulting from the summated effects of the several peripheral effector organs activated by the cooling stimulus. Each cooling load is sufficiently heavy to recruit most if not all effector organs available for resisting core hypothermia and, at the same time, to eliminate any counteracting influences that may be operational when the cooling load is mild or when only a portion of the body is cooled. In addition, the cooling load situations mentioned above are sufficiently heavy for obtaining an insight into capacity without overreaching physiological limitations.

Dependence upon Nerve Fibers Descending from Hypothalamus

It has long been known that physiological resistance to a core hypothermia, as described above and illustrated in FIGURE 1, is due to central nervous system integrative activity. The literature is replete with experimental data that support this conclusion. Representative blocks of crucial information based on the use of chronic preparations are as follows. Pinkston *et al.*[1] demonstrated that removal of the cerebral hemispheres does not alter materially the animal's tolerance to cold exposure. Dusser de Barrene[2] and Bazett *et al.*[3] found that removal of all central nervous system tissue cephalad to the diencephalon does not obviously disturb the cat's ability to maintain body temperature. Bazett and Penfield[4] originally and, most recently, Bard,[5] using the Sherrington method of decerebration, demonstrated that physiological resistance to cold exposure is permanently eliminated in the cat when the diencephalon is removed as a part of the decerebration procedure. Sherrington[6] demonstrated that the spinal dog was unable to prevent a lowering of its core temperature when it was placed in a cold storage room held at 1° to 2° C., whereas an unoperated dog placed alongside maintained thermal balance with ease. The higher the spinal transection, the greater the impairment. In addition, shivering never occurred caudal to the level of transection even though spinal reflexes were fully recovered; thus, a *spinal* subsidiary mechanism subserving resistance to cold does not exist. Similarly, Keller and Blair[7] have demonstrated the nonexistence of such subsidiary medullary mechanism.

I shall use individual protocols from my operated dog series to demonstrate absolute dependence of physiological resistance to a core hypothermia not only on the central nervous system, but upon the hypothalamus in particular.

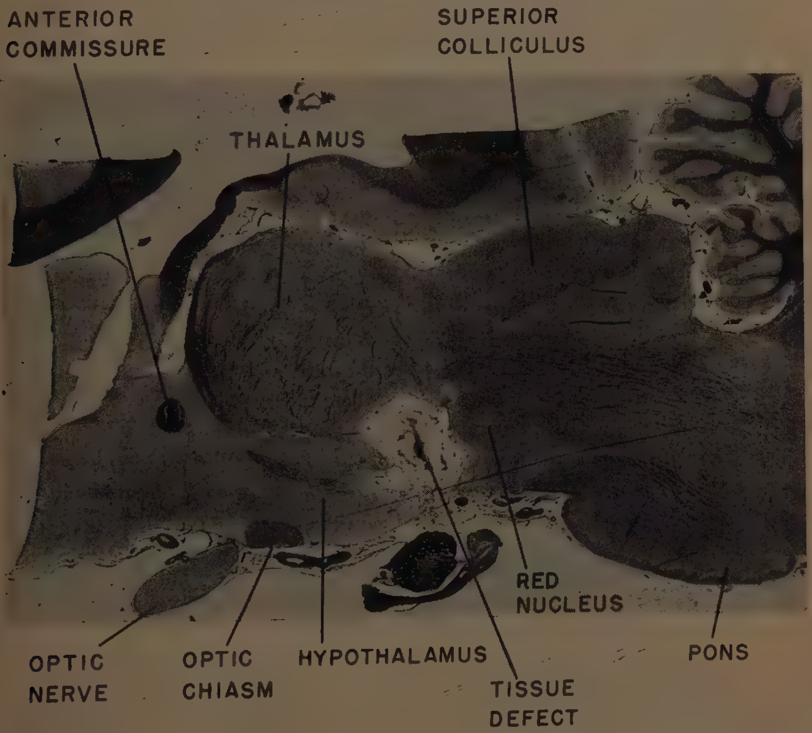

FIGURE 2. Photograph of a Pal-Weigert sagittal section taken from the series on dog 447, showing the location and extent of the tissue defect.

A photograph of a Pal-Weigert sagittal section taken from the series on dog 447 is shown in FIGURE 2. The tissue defect is located in the space previously occupied by the junctional tissue between the hypothalamus and midbrain, whereas the hypothalamus remains largely intact. The cooling curve for this dog when it was subjected to a 3° C. air temperature test situation is shown in FIGURE 3. As indicated at the bottom of the chart, it was necessary to house this animal in an air temperature of 29° C. to maintain its core temperature at the normal 38° C. range. When it was abruptly subjected to the 3° C. cooling load, body temperature fell progressively to the neighborhood of 28° C. in 3 hours. There was no shivering. When the animal was removed to a 23° C. air temperature, core temperature remained at the 28° C. level; there was no spontaneous rewarming.

The foregoing features characterize the deficit in the dog that predictably follows (in the chronic state) a total removal of the posterior half of the hypothalamus or any tissue defect so placed as to sever the nerve fibers exiting caudally from the hypothalamus.

When the tissue defect is confined to hypothalamic gray, but a portion of this gray lying caudal to the defect escapes being coagulated, some physiological resistance to cold also remains. To illustrate this point, photographs of Pal-Weigert sections taken from the series on dog 79 are shown in FIGURE 4. The upper section is through the plane of the left mammillothalamic tract. Note the accomplishment of a selective total hypothalamectomy at this plane; note particularly that no hypothalamic gray tissue remained caudal to the tissue defect. The lower section is through the plane of the right mammillothalamic tract; here a small amount of intact hypothalamic gray is located caudal to the defect. The cooling curve for the dog is shown in FIGURE 5. Note that the body temperature fell in a straight line, but

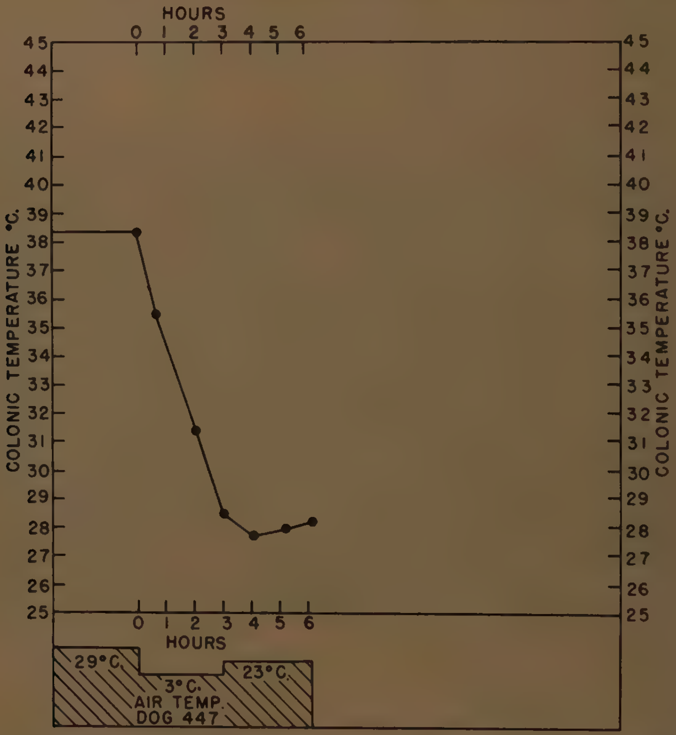

FIGURE 3. Deep colonic temperature curve for dog 447 subsequent to the severance of all nerve fibers exiting caudally from the hypothalamic gray. This was accomplished by the tissue defect shown in FIGURE 2. The unbroken line in the temperature curve indicates the absence of shivering. The rate of cooling exhibited here constitutes the maximal deficit encountered in the chronic state following the placing of large hypothalamic tissue defects.

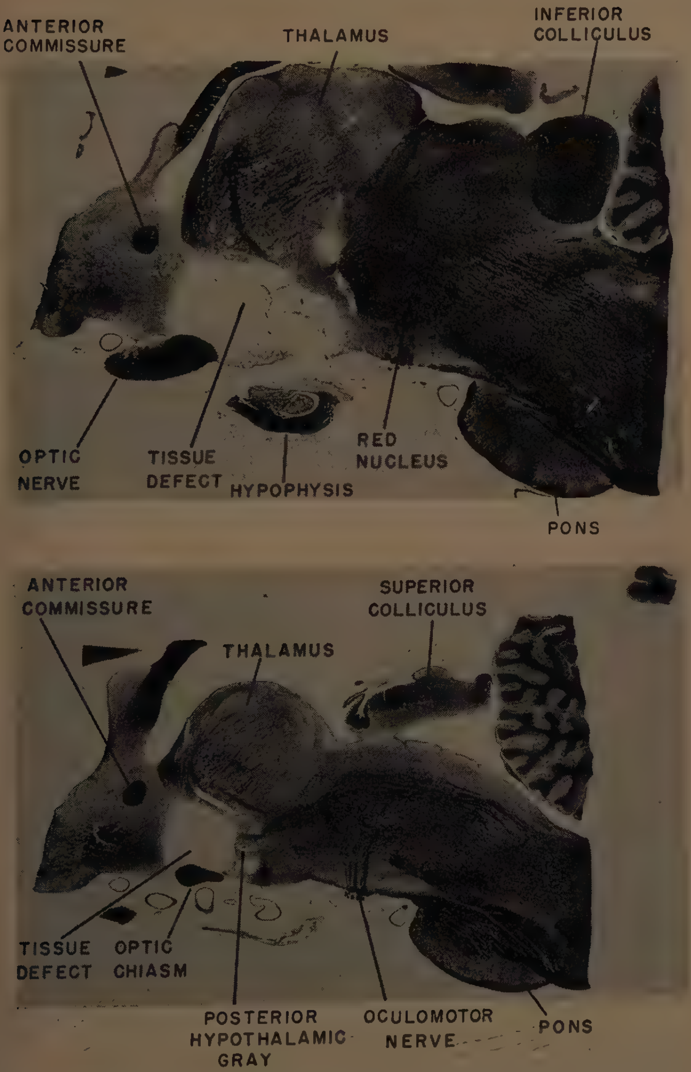

FIGURE 4. Photographs of Pal-Weigert sagittal sections taken from the series on dog 79, showing the location and extent of the tissue defect. The upper section is to the left; the lower section, to the right of the midline.

slightly more slowly than in the instance of dog 447; it took 4 hours rather than 3 to cool to 28° C. There was no shivering, but remnantal spontaneous rewarming was evident. Oxygen consumption determinations have shown that the slower cooling rates and rewarming ability in such preparations are due to remnantal cold-stimulated nonshivering thermogenesis.[8]

A considerably greater remnantal resistance to cold than in dog 79 was retained in dog 96, as shown by its cooling curve in FIGURE 6. Although it was unnecessary to incubate this dog to enable it to maintain a core temperature of 38° C., there was a distinct early deficit, even though shivering was prominent, with a leveling off between 32° and 31° C. Spontaneous rewarming was evident in the presence of the cooling load.

A retention of considerable resistance to cold (a marginal deficit) was shown in dog 37, as evidenced by the cooling curve in FIGURE 7. Only a mild hypothermia resulted during the first 5 days of exposure, but an abrupt lowering of core temperature occurred during the sixth day. Shivering was always prominent. The dorsal half of the right lateral segment of the posterior hypothalamic gray remained undisturbed in this preparation.

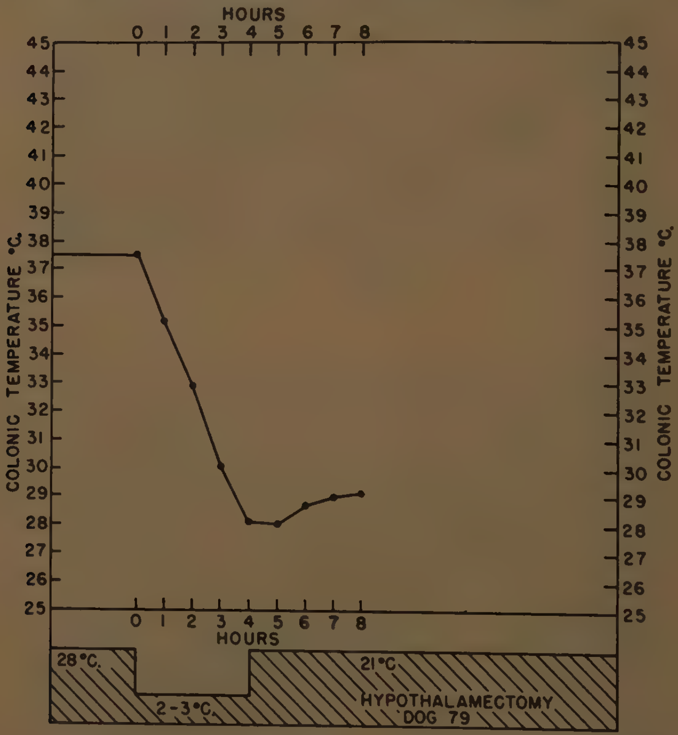

FIGURE 5. Cooling curve for dog 79, which was totally hypothalamectomized except for a small remnant of hypothalamic gray located caudal to the tissue defect. The slower rate of cooling and the postexposure spontaneous rewarming evidences the retention of remnantal physiological resistance to cooling. The unbroken line in the temperature curve denotes the absence of shivering.

The foregoing experiments verify and extend the well-documented conclusion that the homotherm's ability to prevent a lowering of its core temperature is dependent upon a neural integration that activates the peripheral effector organs utilized with nerve impulses that are efferented from the hypothalamus. Subsequently I shall refer to this efferent outflow from the hypothalamus as the resistance-to-hypothermia outflow.

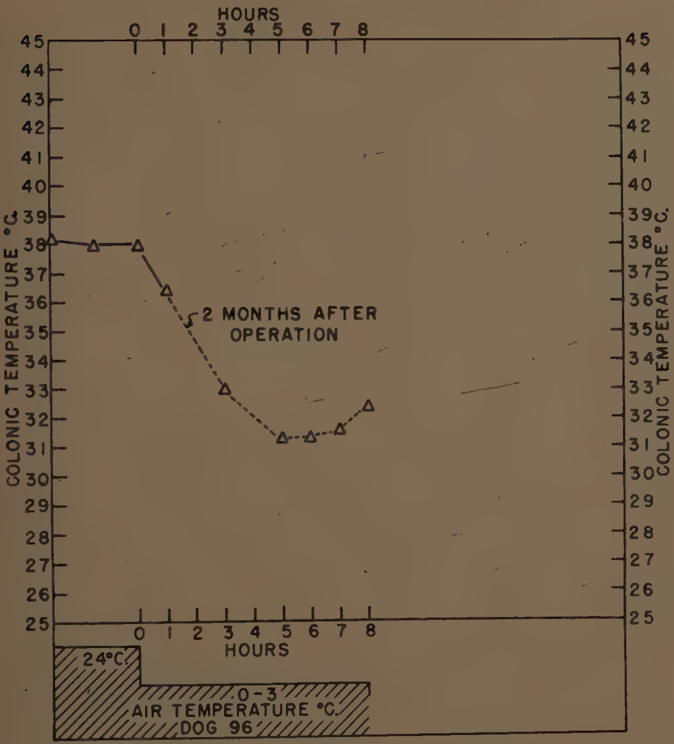

FIGURE 6. Cooling curve for dog 96, illustrating a sizable deficit with retention of considerable resistance to cooling following a massive hypothalamic tissue defect. Note that resistance to cooling increased strikingly after core temperature reached the region of 31° C. Also note that the cooling rate did not decrease until some time after shivering was activated.

Problems that remain to be elucidated are: (1) a more detailed cataloguing of the peripheral effector organs activated by the resistance-to-hypothermia outflow and (2) determining the detailed mechanics of the responsible neural integration.

Not Dependent upon Direct Endocrine Support

In the category of cataloguing peripheral effector organs, we have been concerned with the question as to whether acute cold exposure elicits immediate endocrine responses and, if so, whether such responses are utilized as processes playing a direct role in physiological resistance to cold. These questions are not new; they are old with respect to their first appearance in the literature and old to many in terms of personal investigative efforts.

My interest in them was potentiated when no discernible endocrine deficits were found in dogs rendered permanently poikilothermic against cold by a tissue defect that was confined to the caudal aspect of, or lay caudal to, the hypothalamus (dog 447).[8] Such an animal exhibits (1) an energy metabolism in the normal range when body temperature is maintained near 38° C., (2) an insulin tolerance that is not materially altered from the preoperative status, (3) an ability to withstand major surgical traumas such as total pancreatectomy and total sympathectomy without endocrine supportive measures, (4) a full-blown diabetes mellitus following total pancreatectomy, and (5) at autopsy, adrenal cortices that are not atrophied. The foregoing status also obtains following complete transection of the brain stem at any level of the midbrain or pons, and also following a total midbrainectomy.

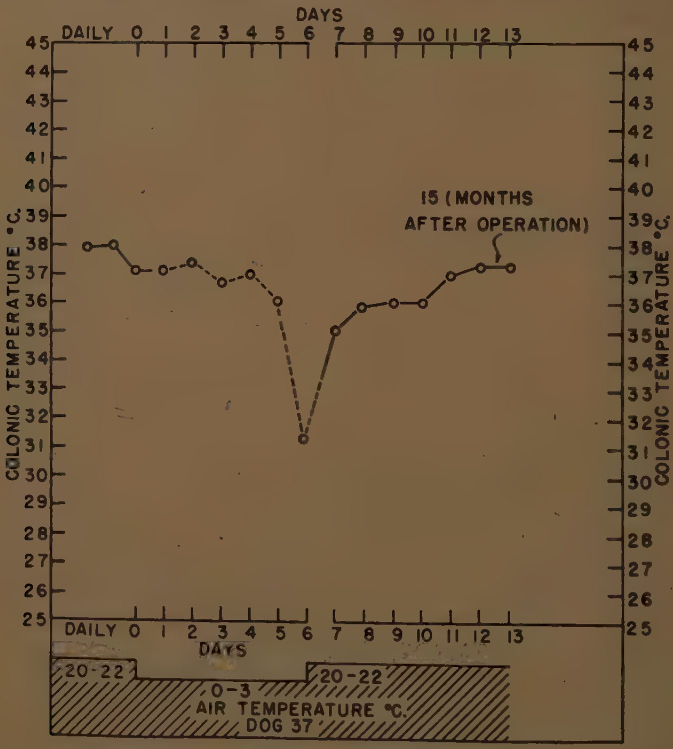

FIGURE 7. Core temperature curve for dog 37 before, during, and after a 6-day exposure to a 3° C. air temperature. Note that a definite deficit did not become evident until the sixth day of exposure.

Establishment of the foregoing fact caused me to wonder how hypophysectomized and adrenalectomized dogs would respond to cooling loads. The core temperature and blood glucose responses of a hypophysectomized dog that exhibited maximal panhypopituitarism to a −20° C. air temperature are charted in FIGURE 8. The core temperature rose and was maintained slightly above 38° C. for the first 5 hours. At the end of the seventh hour, it had fallen slightly below 38° C. and, during the first hour after removal to a neutral environment, it fell farther and more rapidly. Shivering was prominent throughout the 8-hour period. The beginning low blood-sugar level was elevated somewhat at the end of the first and second hours, but a precipitous fall occurred between the second and third hours. However, it was not sufficiently low at this time for the animal to exhibit hypoglycemic symptomatology. At this time glucose and milk were fed. At the end of the seventh hour blood sugar was extremely low and the animal exhibited a definite hypoglycemic symptomatology. Glucose was given intravenously and regular food subsequently. To be emphasized are the facts that core temperature was not affected by a low blood-sugar level until hypoglycemic symptomatology was in evidence and that, with the onset of hypoglycemic symptomatology, core temperature began to descend before the disappearance of shivering.

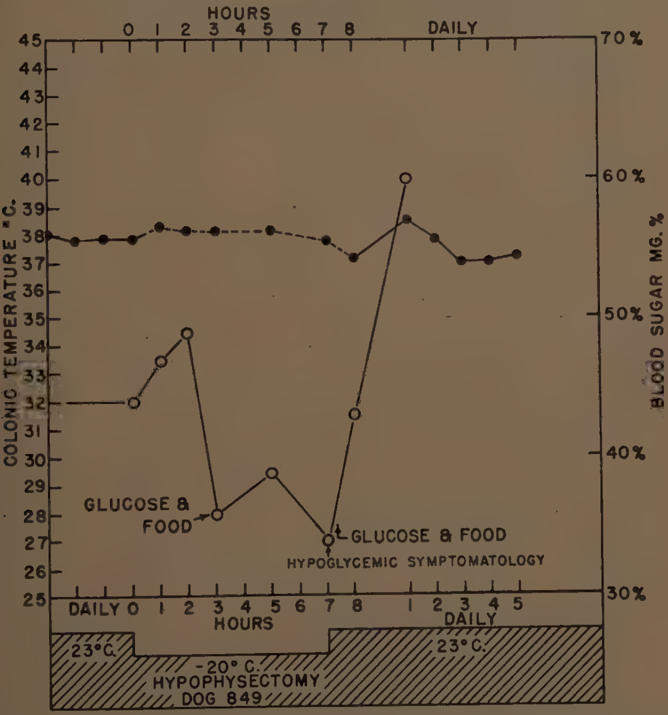

FIGURE 8. Core temperature and blood glucose curves on hypophysectomized dog 849 before, during, and after exposure to a −20° C. air temperature. These responses are representative for hypophysectomized preparations.

The core temperature and blood glucose responses of an adrenalectomized dog (maintained with an implanted pellet of desoxycorticosterone) during exposure to a 3° C. air temperature for a period of 15 hours are graphed in FIGURE 9. Note that there was no tendency for core temperature to drop until between the twelfth and fifteenth hours, when it fell from slightly above 38° C. to near 35° C. When temperature was taken at the end of fifteen hours, there was no shivering and hypoglycemic symptomatology was present. Glucose was administered intravenously and food was given.

Recovery from hypoglycemic symptomatology was immediate. Shivering was present an hour later and core temperature rapidly returned to normal. Here again the fall in body temperature was definitely associated with a hypoglycemia sufficiently profound to induce symptomatology. Also in this instance the hypoglycemic symptomatology was of sufficient duration to eliminate shivering.

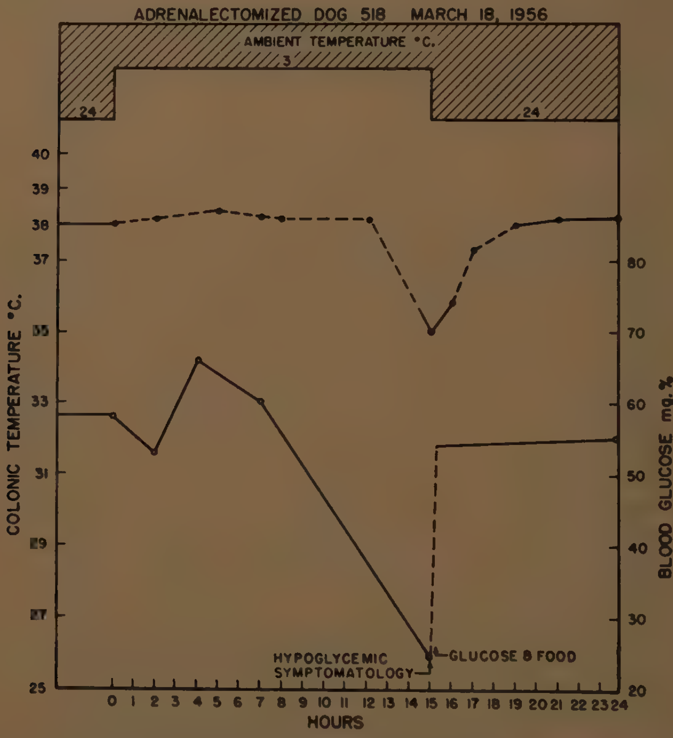

FIGURE 9. Core temperature and blood glucose curves on an adrenalectomized dog during and after a 15-hour exposure to a 3° C. air temperature. These responses are representative for adrenalectomized dogs. Prolonged cold exposure induces hypoglycemia in the adrenalectomized dog, but core temperature is maintained until the hypoglycemia is sufficiently heavy to produce clinical symptomatology.

In FIGURE 10 are the core temperature and blood-sugar curves for the same adrenalectomized dog during subjection to the same cooling load for a 3-day period; during this period blood sugar was maintained by periodic feeding. Note that body temperature did not fall below the normal homothermic level (38° C. for the dog). Shivering was prominent throughout the exposure.

It is fully apparent, therefore, that so long as hypoglycemic symptomatology is avoided by appropriate feeding in hypophysectomized and adrenalectomized dogs, physiological resistance to cold is entirely adequate for the cooling loads illustrated. These results are compatible with the interpretation that there are no hypophysial or adrenal activities directly associated with the sequence of physiological responses that collectively prevent a core hypothermia from occurring during acute exposure to moderately heavy cooling loads. However, when there is need for body tissue to be converted (gluconeogenesis is a known example) to available fuel for thermogenic purposes, the activities of these endocrine organs are recruited. The need for gluconeogenesis is the specific hypophysial-adrenocortical activating stimulus, not cold as such. In the presence of an adequate food intake, the hypophysial-adrenocortical-stimulated gluconeogenesis is not recruited. The mechanisms involved in tissue conversions are, of course, markedly impaired in these preparations.

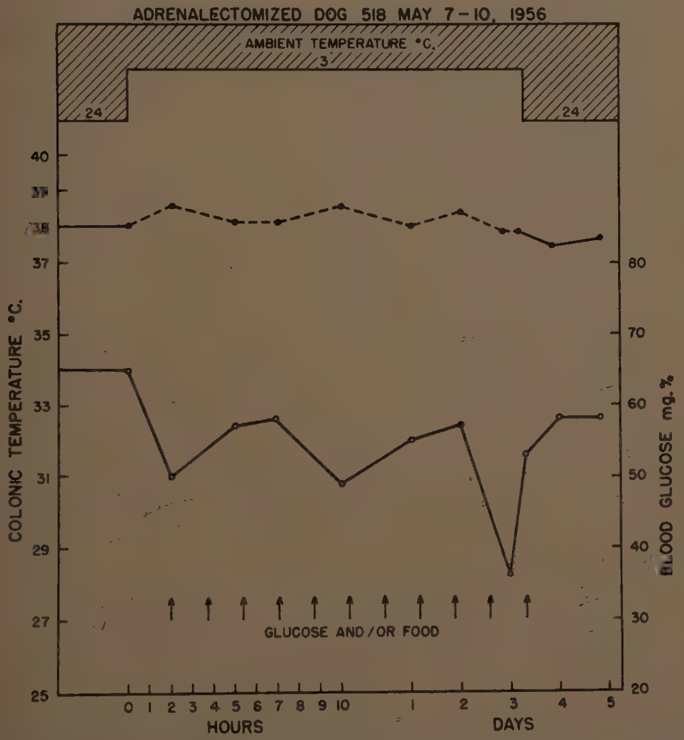

FIGURE 10. Core temperature curve on an adrenalectomized dog, in which the blood glucose level was maintained by periodic feeding, during a 3-day exposure to a 3° C. air temperature. Hypoglycemic symptomatology was not present at any time during, or subsequent to, the exposure.

In addition, cooling loads of the magnitude described above do not precipitate adrenal insufficiency crises in either hypophysectomized or adrenalectomized dogs as long as severe hypoglycemic symptomatology is not allowed to persist over an extended period of time. This is manifested both by (1) the absence of changes in serum sodium and potassium and (2) survival without adverse symptomatology following cold exposure without the administration of hypophysial or adrenocortical substitution therapy. Both these preparations are exceedingly prone to adrenal sufficiency crises. Therefore insofar as hypophysial or adrenocortical activity is concerned, moderate cold is a benign rather than a malignant systemic stimulus; as a nonspecific systemic stimulus, cold definitely should not be included in the same category with trauma and infection.

The foregoing interpretation correlates perfectly with that of Nelson *et al.*, who found an absence of corticosteroids and catechols in the adrenal venous blood of unanesthetized dogs during exposure to moderately heavy cooling loads. The fact that severe cooling loads do activate the adrenals is attested to by the work of Egdahl and Richards,[10] but even in this situation the stimulus is not as vigorous and sustaining as in the case of trauma Thus, even severe cold appears not to be a direct, nonspecific systemic stimulus. Severe cold, of course, can and does serve indirectly as such a stimulus when it becomes the trauma- (cold injury) producing agent.

Mechanics of the Neural Integration

In the category of the detailed mechanics of the central nervous system integration, there have long been good reasons for supposing that the resistance-to-hypothermia outflow can be activated in either of 2 ways: (1) by chilling body tissues lying peripheral to the brain (peripheral receptors) or (2) by chilling a localized area of the brain (central or brain receptors) Whether this is true and, if so, to what extent and under what circumstances each contributes to the over-all activations of the outflow has been, and continues to be, difficult to ascertain. Each of these possibilities can best be examined separately.

Can the resistance-to-hypothermia outflow be activated and driven by cold-sensitive elements located in tissues lying peripheral to the central nervous system? An affirmative answer to this question is attested by the following representative experiments.

First, there is the cold-bath experiment. To quote Bazett:[11] "If a man is immersed into a cold bath, an initial rise in deep body temperature occurs and shivering commences during this rise. Shivering must, therefore, in this situation be reflexly activated because it cannot be dependent upon a nonexistent fall in brain temperature."

Second, this conclusion is reinforced and extended by two case histories from my experimental series. One describes a healthy mongrel dog placed in a −20° C. air temperature. The core temperature rose rapidly to, and was maintained at, 39° C. for the duration of a 24-hour exposure. Shivering was prominent throughout the exposure.[8] The other case history is that of a totally sympathectomized dog placed in a 3° C. air temperature for 3 days. The test was run 5 months after the total sympathectomy.[12] On exposure, the core temperature dropped from 39 to 38° C., where it was maintained for 7 hours, but the next morning it had risen to almost 40° C. It was maintained at this level for the succeeding 2 days. Shivering was prominent throughout the exposure.

In these situations the entire resistance-to-cold outflow was reflexly activated and driven by a cold body shell because it could not have been activated by a "nonexistent fall in brain temperature." Even more important is the fact that the reflex response driven by chilling the body shell was definitely prepotent over inhibition by core temperatures of 39 and 40° C., respectively.

Third, there is the experiment of Davis and Meyer in the rat,[13] where body core temperature was selectively and progressively raised by microwave, while shell temperature was maintained at a low level by exposure to cold air. Shivering was prominent and continued until core temperature reached the neighborhood of 40° C., at which time it stopped simultaneously with the activation of heat dissipation outflow. In this experiment shivering obviously was driven reflexly from the cold body shell until core temperature became the prepotent variable.

To. what extent the resistance-to-cold outflow can be activated reflexly by chilling deep body tissues lying peripheral to the brain (peripheral core) largely remains an open question. The work of Cort and McCance[14] and Forster and Ferguson[15] evidences or suggests the reflex activation of components of this outflow by chilling the lower respiratory tract and the stomach area, respectively.

Information pertaining to circumstances under which the resistance-to-cold outflow can be reflexly inhibited is also limited. Uprus *et al.*,[16] Hemingway,[17] and others have demonstrated that this outflow can be inhibited with ease as soon as the driving cold stimulus is withdrawn. The Uprus group believed that their experiments evidenced a blood temperature (brain receptor) inhibition, but it seems to me that their results are more compatible with a reflex basis interpretation. Hemingway was careful not to rule out a reflex explanation for the inhibition obtained in his experiment.

Can the resistance-to-cooling outflow be activated and driven by cold-sensitive elements localized in the brain: that is, without assistance from afferent influx? That this can occur has long been assumed on the basis of convincing but nevertheless presumptive evidence.

First, there are the carotid blood-cooling experiments.[18] However, there always remained the possibility that the resultant responses could have been occasioned reflexly by the cooled blood activating receptors located in the peripheral tissues of the head. Indeed, Strom[19] reports: "It was found that these means (carotid blood) of cooling were quite ineffective for lowering the temperature of the hypothalamus even if the temperature of the skin of the head and buccal mucosa was markedly lowered."

Second, there are the experiments in which direct cooling of localized areas of the brain clearly caused peripheral vasoconstriction and a rise in peripheral core temperature.[20] The question arises here as to whether cold (because of the degree of cold used, 10° C. in Barbour's experiment) might be a nonspecific rather than a specific stimulus. Assuming that specific cold-sensitive brain receptors exist, little information has been gained relative to thresholds because of ignorance of the distances obtaining between the cooling source and the brain receptive element. Moreover, some of these experiments were complicated by the use of anesthesia. Anesthetics are notorious for changing threshold values. Reasonably correct threshold values would be necessary before it could be ascertained whether responses elicited in this manner were within practical physiological ranges. True thresholds cannot be determined until the receptive element is crucially localized. The failure to obtain responses following localized brain-cooling experiments have caused some investigators to question the existence of cold-sensitive brain receptors.[19] However, such a failure may be due to such factors as (1) the use of anesthetized preparations: the fact that anesthesia paralyzes the resistance-to-cold outflow was known prior to the work[21] of Simpson, (2) an incorrect supposition as to receptor localization, or (3) a diffuse spread of the receptive elements over a large area. For instance, there is no assurance that the cold-sensitive elements are localized in the hypothalamus; quite the contrary, the work of Barbour and other early investigators suggests a prehypothalamic localization.

Third: perhaps the most convincing evidence that the resistance-to-cooling outflow can be activated and driven by cold-sensitive brain elements, as originally and continually suspected, is inherent in my observations on the isolated pyramidal bundles preparation.[22] In this preparation the brain stem is completely transected through the lower pons except for sparing the pyramidal bundles. The core temperature and shivering responses of such a preparation to a 10° C. air temperature cooling load is shown in FIGURE 11. Subsequent to the operation, the animal was housed at 25° C. air temperature. Note that on the morning after operation the core temperature was 37° C. There was no shivering. During the first hour of exposure, colonic temperature fell from 37° C. to 35° C., at which point shivering was activated and core temperature ceased falling. At the end of 6 hours body temperature had risen to 38° C., when the animal was returned to the 25° C. air temperature. Core temperature then rose rapidly to reach 40° C., where it plateaued. Shivering continued prominent even after body temperature plateaued.

Although there has been some variability in the preparations observed, nevertheless they have all exhibited (1) a near-normal resistance to cooling, and (2) a remarkable consistent overshooting of core temperature during or immediately subsequent to removal from moderately heavy cooling loads. These features are readily evident in FIGURE 11; also in FIGURES 2 and 3 of my previously published work.[22]

It is obvious, therefore, that nerve fibers subserving resistance-to-cold functions descend in the pyramidal bundles at the level of the pons. I hasten to point out that these fibers must, of necessity, join these bundles somewhere caudal to the hypothalamus; it is also reasonably certain that all resistance-to-cold fibers do not course with these bundles at the level of the pons and upper medulla.

Most important is the fact that inherent in these experiments is proof positive that the resistance-to-cold outflow can be activated and driven by cold-sensitive elements localized in the brain without assistance from afferent influx from peripheral receptors. This is true provided that afferent fibers subserving thermal reflexes do not course cephalad in the unsevered pyramidal bundles or enter the brain through the intact trunks of the first, second, and third cranial nerves. These possibilities seem remote; nevertheless, they must be crucially investigated in this connection. Brodal and Walberg[23] have demonstrated fiber degeneration in the pyramidal bundles following experimental lesions placed at spinal levels. It is reasonably certain that some of this degeneration, and perhaps all of it, is retrograde in nature. Patton and Amassian[24] question the presence of ascending fibers in the pyramidal bundles on the basis of electrophysiological techniques, but they did not investigate thermal stimuli.

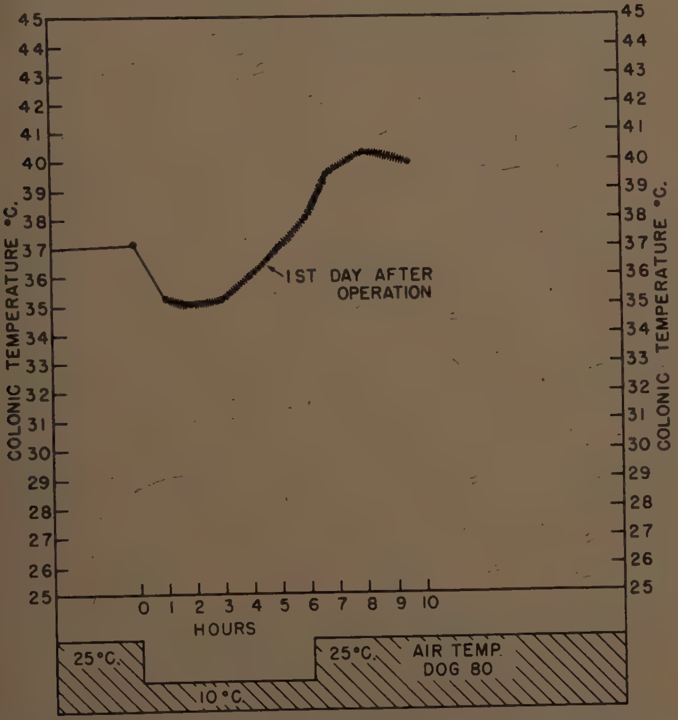

FIGURE 11. Colonic temperature response of an isolated pyramidal bundles preparation during and after exposure to a 10° C. air temperature. The cross lines denote the presence of shivering.

The characteristic rise in core temperature to 40° C. and even to 41° C. before plateauing during and subsequent to moderately heavy cooling loads in these preparations has intrigued me. I wonder if perhaps this feature might afford an insight into the detailed mechanics of the neural integration. Assuming that resistance-to-hypothermia outflow is completely deafferented in the isolated pyramidal preparation, this characteristic overshooting would be compatible with the following interpretation. Normally, the resistance-to-hypothermia outflow is activated either reflexly or by cold-sensitive brain receptors, or by a potentiating combination of both, depending upon the particular situation at the time of onset of the cooling load. Once activated, this outflow continues to discharge until it is actively inhibited. In the absence of inhibiting afferents from the periphery, core temperature rises to the neighborhood of 40° to 41° C. when the outflow is inhibited reciprocally as the heat dissipation outflow is activated when blood temperature reaches the threshold for the heat-sensitive receptors located in the brain. This overshooting feature becomes apparent because the isolated pyramidal preparation is completely poikilothermic to heat (FIGURE 12); all heat-dissipation efferent fibers are completely severed. However, the heat-sensitive

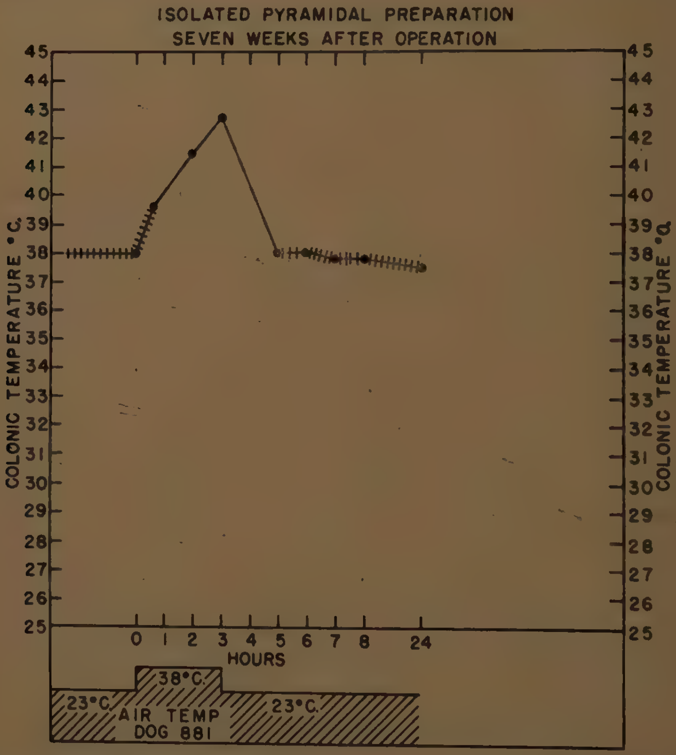

FIGURE 12. Colonic temperature and shivering responses of an isolated pyramidal bundles preparation during and after warming to 43° C. Cross marks denote the presence of shivering.

receptors located in the brain and the appropriate reciprocal synaptic connections with the resistance-to-hypothermia outflow are not disturbed by the much more caudally situated pontine transection.

The foregoing interpretation is strengthened by the experiment illustrated in FIGURE 12, which was performed on a chronic isolated pyramidal bundles preparation. This test was run 7 weeks after operation. On the morning of the test core, temperature was 38° C. and shivering was present. The animal was warmed by placing it in a 38° C. air temperature. Shivering continued until core temperature reached 39.8° C.; simultaneously, with the cessation of shivering, there occurred a noticeable relaxation in muscle tonus. Immediately the animal warmed less rapidly, as shown by the change in slope in the core temperature curve. Subsequently, as the animal was allowed to cool in an air temperature of 23° C., colonic temperature fell progressively until it reached 38° C. where, abruptly, body temperature plateaued and shivering was again observed.

The foregoing emphasizes the fact that there is every reason to continue to suppose, as did earlier investigators, that the resistance-to-cooling outflow can be activated and driven by cold-sensitive receptors located in the brain, as well as by cold receptors lying peripheral to the brain. The location of the cold-receptive element in the brain remains an open question. However, presupposing that the brain cold-sensitive element is separate and distinct from the outflow cell, the resistance to cold manifested by the hypothalamic preparation (brain-slicing procedure) could well be entirely a peripheral receptor-driven affair, whereas the resistance manifested by the isolated pyramidal bundles preparation could be entirely a prehypothalamic brain receptor-driven affair. Such a location for the cold-sensitive elements in the brain is compatible with both brain cooling and puncture hyperthermia experiments.

Finally, there is no cogitable reason to suspect that the neural integration involved in physiological protection against cold is in any way different from other neural integrations. Specificity of receptive elements, prepotency of reflexes (whether initiated peripherally or centrally), reciprocal innervations, and potentiating and depressing influences such as (1) the nonspecific effect of temperature on neural thresholds and conduction rates and (2) nonthermal facilitating and inhibiting influences are all factors that modify responses and make any neural integration adaptable to variable situations.

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PROTECTIVE EFFECTS OF HYPOTHERMIA AGAINST PATHOLOGICAL PROCESSES OF THE NERVOUS SYSTEM*

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Preliminary to the presently reported experiments, studies were conducted in which the effects of hypothermia on normal physiology of the nervous system were investigated. They served as a basis for subsequent studies of the effect of temperature reduction on pathological processes, as well as for the use of hypothermia in the clinical practice of medical and surgical neurology. Therefore I propose to review briefly this work as an introduction to the body of this paper.

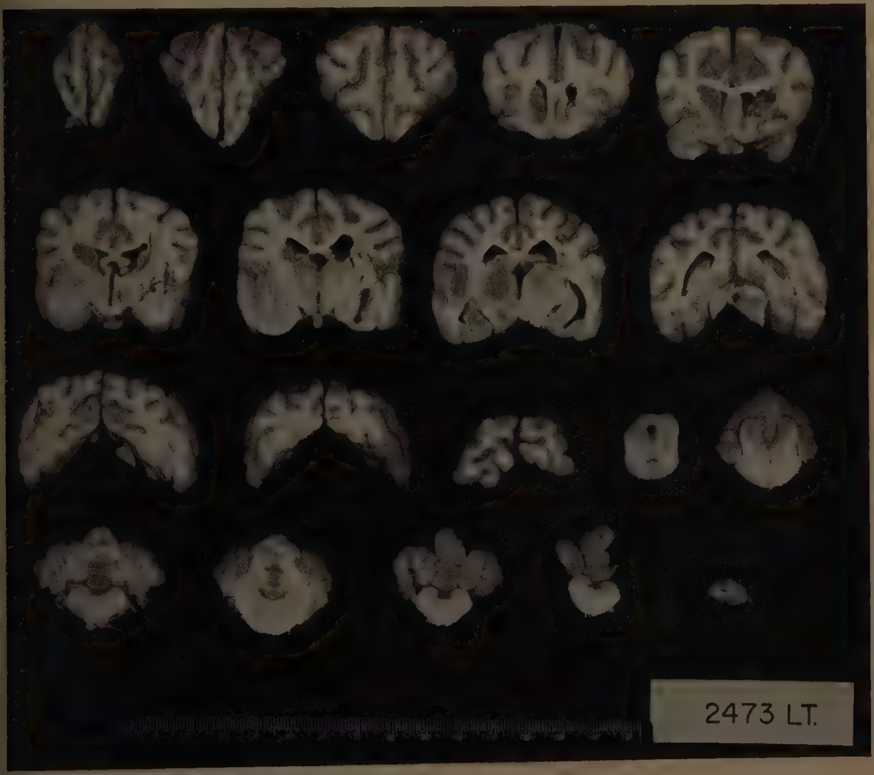

FIGURE 1. Coronal sections of a dog brain following transection of the left middle cerebral artery at normal body temperature. Reproduced by permission from the *Journal of Neurosurgery.*

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It was demonstrated first that as temperature is reduced there is a reductio in cerebral metabolism at a rate of 6.7 per cent/°C. of the precooling value There is a corresponding decrease in cerebral blood flow.[1] Mean blood pressure is also diminished, but at a slower rate, 4.8 per cent/°C. Cerebrovascular resistance is increased. Brain volume is reduced during hypothermia s

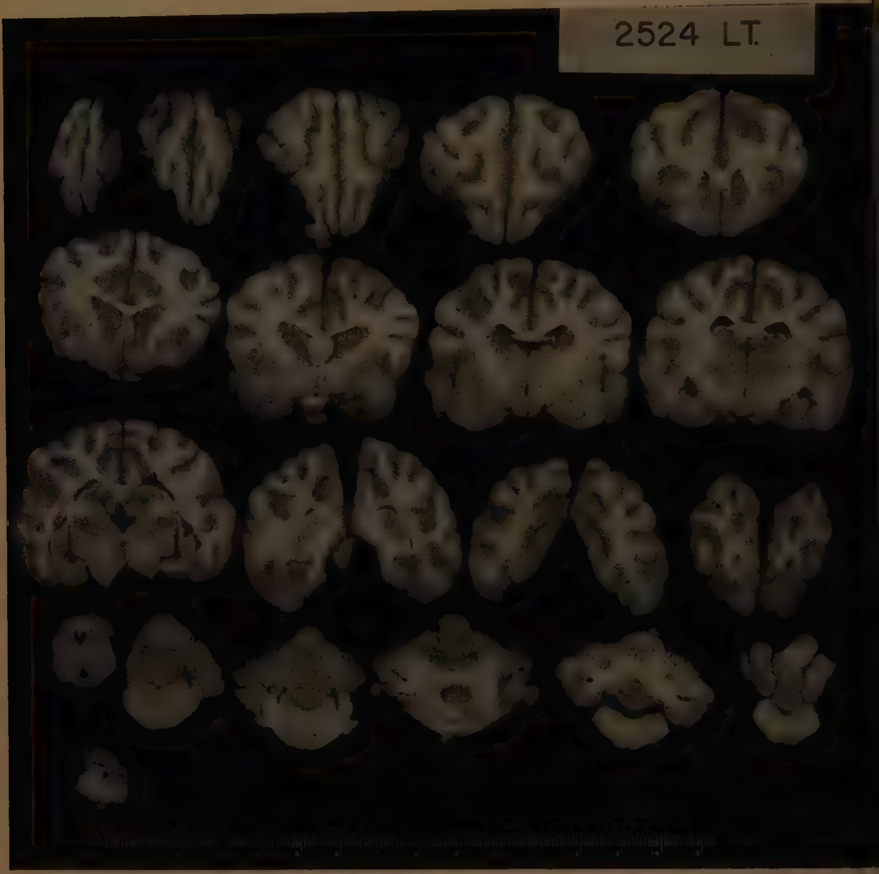

FIGURE 2. Coronal sections of a dog brain following transection of the left middle cerebral artery during hypothermia. Reproduced by permission from the *Journal of Neurosurgery.*

that at 25° C. brain size is decreased 4.1 per cent, while the extracerebral space—that intracranial space not occupied by brain—is increased 31.8 per cent.[2] Cerebrospinal fluid pressure and venous pressure are reduced at a rate of 5.5 per cent/°C.

It may be seen, therefore, that temperature reduction produces a medley of effects that conceivably could prove useful in the study and treatment of abnormal processes within the nervous system. In particular, I refer to the application of a temperature-induced reduction in metabolism to the problem of cerebral anoxia and to the application of temperature-induced reduction in intracranial pressure and brain volume to the problems of increased intracranial tension resulting from trauma or other pathological states.

Attention was directed initially to the effect of hypothermia on cerebral vascular insufficiency. It was postulated that a marked reduction of cerebral metabolism at the time of a vascular occlusion would provide more advantageous conditions for the establishment of collateral circulation, thereby resulting in the modification or prevention of infarction. It was thought that such conditions might be attained by the use of hypothermia.[3]

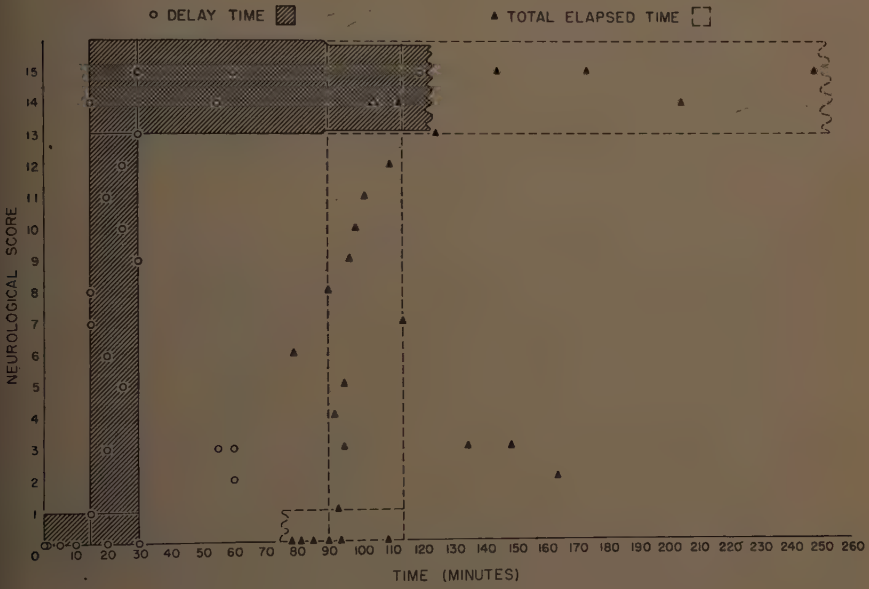

FIGURE 3. Effect of hypothermia following interruption of the middle cerebral artery upon the neurological score; the higher the score, the greater the neurological disability. Reproduced by permission from the *A.M.A. Archives of Neurology and Psychiatry.*

The middle cerebral artery of 30 dogs was occluded permanently by surgical transection or resection. In 15 of these animals, the body temperature was maintained at normothermic levels. These dogs served as the normothermic controls. Coronal sections of the brain of a control normothermic animal are seen in FIGURE 1. A marked distortion and disruption of the architecture may be seen that involves the basal ganglia, internal capsule, thalamus, hypothalamus, visual pathways, and parts of the overlying frontoparietal-temporal cortex.

Fifteen dogs were subjected to the same procedure during hypothermia. They were kept at a body temperature of 22° to 24° C. for 1 hour only, and then were rewarmed and observed for 3 weeks before sacrifice. Coronal sections of the brain of a hypothermic dog are seen in FIGURE 2. This brain is intact except for a microscopic infarct in the hypothalamus and a small cyst in the pyriform lobe resulting from trauma during surgery.

The next question to be answered was whether hypothermia would be of value if the middle cerebral artery were to be occluded at normal body temperature and if hypothermia were then induced. This would be equivalent to the treatment of a cerebrovascular accident with hypothermia. Experiments designed to answer this question yielded[4] the following results (FIGURE 3). It was demonstrated that protection against infarction could be obtained if hypothermia was induced within 15 min. of the occlusion of the artery and if a level of 24° C. or less was attained within a total elapsed time of 90 min. If these times were exceeded, a secondary zone was entered for which the delay time was 15 to 30 min. and the total elapsed time, 90 to 114 min. Here the results were unpredictable; some animals were well protected, others were not. Beyond these periods no benefit was observed.

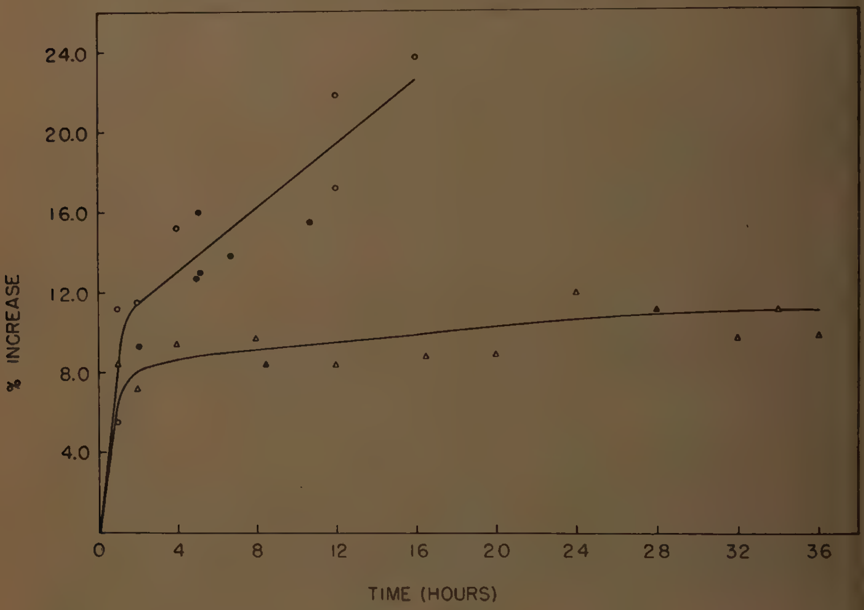

FIGURE 4. Graph of the percentage increase of size of the injured hemisphere as compared with the uninjured hemisphere, plotted as a function of time. Circles represent normothermic dogs; triangles represent hypothermic dogs. Open symbols represent animals that were sacrificed; closed symbols represent animals that died. Reproduced by permission from the *Journal of Neurosurgery*.

Because of the decrease in brain volume consequent to the induction of hypothermia, it was felt that this technique might be of value in conditions where cerebral edema is a prominent feature, as in severe head injuries. A method was developed by which standardized brain injuries could be produced.[5] Equivalent lesions were produced in normothermic and hypothermic dogs and the degree of posttraumatic brain swelling was plotted (FIGURE 4).

The normothermic animals developed progressive, fulminating edema and died. The hypothermic dogs developed a small amount of edema immediately following the injury, but thereafter progression was minimal up to 36 hours, the longest period of observation. The lesion was circumscribed sharply and resembled grossly a cerebral contusion or hemorrhagic infarction (FIGURE 5). In addition, if sufficient time had elapsed before death, typical posttraumatic secondary changes developed. These were: edema of the entire injured hemisphere, shift of the internal structures across midline, ipsilateral ventricular collapse with contralateral dilatation, transtentorial herniation, incisural and aqueductal block, and brain stem compression, the probable eventual cause of death.

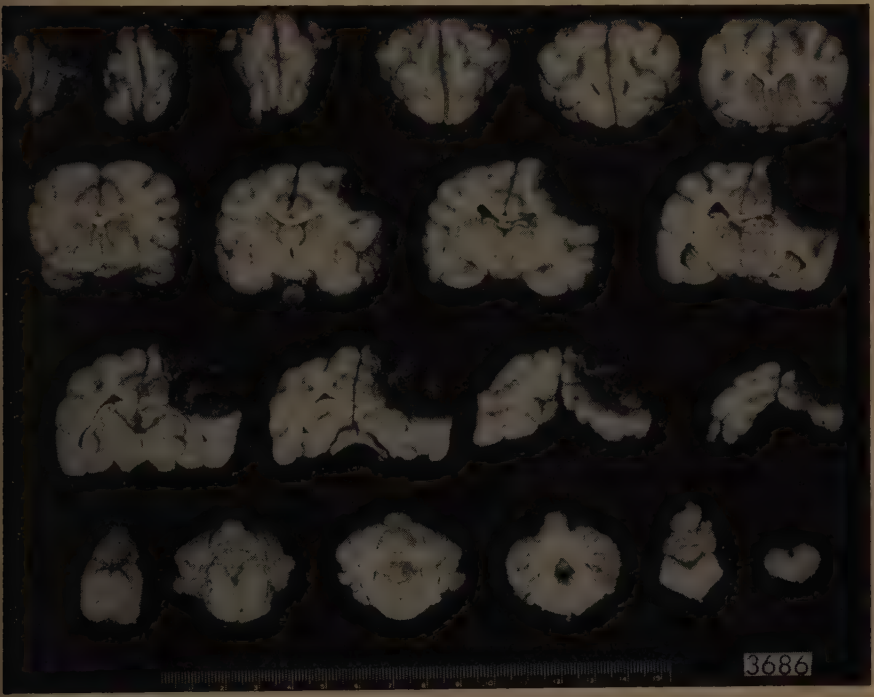

FIGURE 5. Coronal sections of a dog brain, normal body temperature, 7¾ hours after injury. Reproduced by permission from the *Journal of Neurosurgery*.

The identical lesion was produced in dogs with a mean body temperature of 24.1° C. at the time of injury (FIGURE 6). The pathological result was altered. The lesion had a scalloped appearance, with the hemorrhage tending to follow the cortical gray markings while sparing the white matter. Cerebral edema was minimal.

Histologically, the lesions in the normothermic dogs were characterized by widespread destruction of the cellular elements, especially the neurons, with complete loss of cytoarchitectural markings, interstitial edema, vascular dilatation, capillary and venous thromboses, perivascular diapedesis, petechiae, and coalescent hemorrhages (FIGURE 7). If the lesion was more than 4 hours old, an intense inflammatory reaction occurred, polymorphonuclear leukocytic elements predominating, maximum intensity being manifest within 12 hours. In the hypothermic dogs, there was a marked difference in the histological character of the lesions (FIGURE 8). The cortical architecture was better preserved and cellular elements showed less evidence of injury, but definite degenerative changes were found that may or may not have been reversible in nature. Interstitial edema was reduced and vascular dilatation and hemorrhage were much decreased. Cellular destruction and hemorrhage continued to a maximum at 24 hours. It is noteworthy that the inflammatory reaction was still absent or minimal even in lesions 36 hours old, the longest period of observation in this particular study.

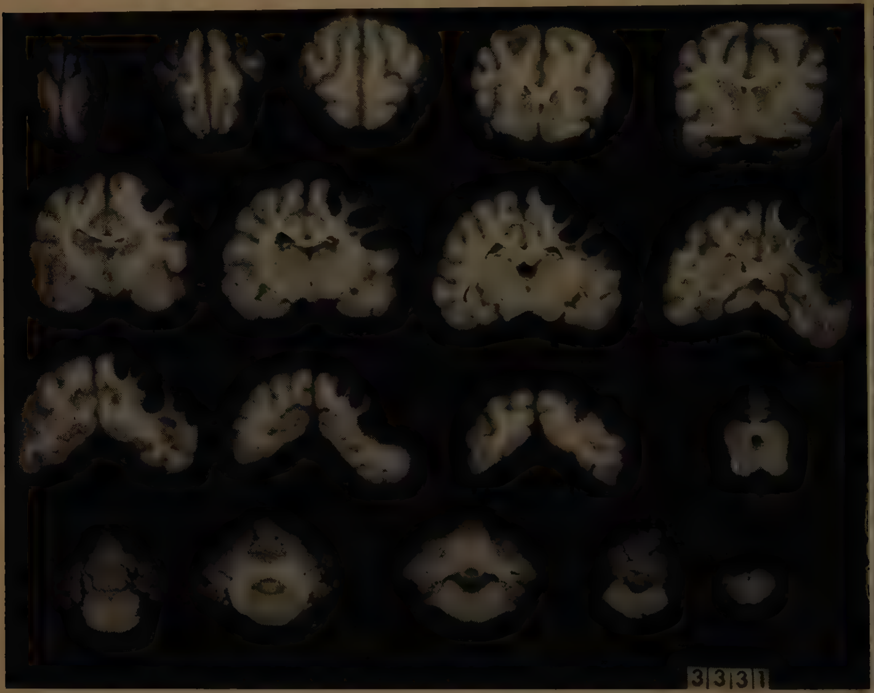

FIGURE 6. Coronal sections of a dog brain, hypothermia, 6 hours after injury. Reproduced by permission from the *Journal of Neurosurgery*.

The effect of hypothermia upon the mortality of acute brain injury was investigated next.[6] To accomplish this, it was necessary to establish first a median lethal-size injury. Various size lesions were produced in 49 normothermic dogs. The results were arrayed into 9 groups and the mortality rates were calculated at their probits. The number killed expressed in probits was plotted against the size lesions in milliliters. Analysis of the probit regression line yielded an LD_{50} of 5.42 ml.

When we had established that a 5.42-ml. lesion could be expected to kill 50 per cent of normothermic dogs, an injury of this size was created in a group of hypothermic animals. The lesions were produced when the body temperature was 25° C. or less, and the dogs were maintained at this temperature for 1 hour. They were then rewarmed and observed for 7 days. Under these conditions, 14 of 15 hypothermic dogs survived. This is a mortality rate of 1 in 15 and is significantly different from that of the normothermic dogs at the 0.01 level.

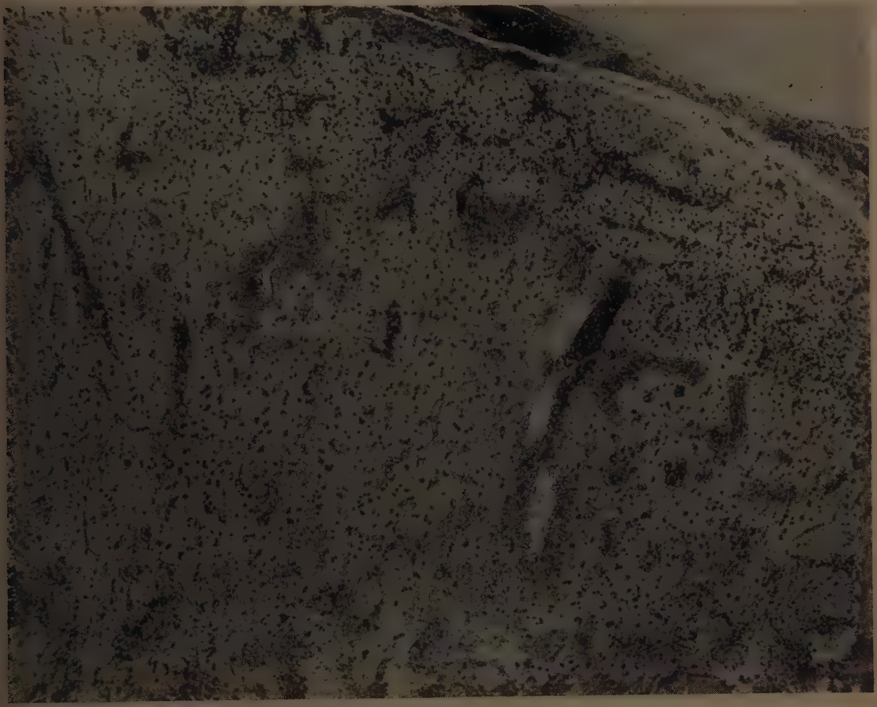

Figure 7. Microphotograph of the lesion, normal body temperature, 12 hours after injury. Cresyl violet stain. Reproduced by permission from the *Journal of Neurosurgery*. × 15.

The brain of each animal in this series was cut and sections were taken at random for histological examination. In brain sections from dogs whose lesions were comparable, it was seen that the inflammatory reaction in the hypothermic dogs was more advanced. That is, the normothermic animals showed a temporal sequence of initial polymorphonuclear leukocytic influx into and about the lesion, followed by the first appearance of lymphocytes in 48 to 72 hours; slight macrophagic and fibroblastic vascular activity became evident at the end of 7 days. By contrast, at 72 hours the hypothermic animals showed marked lymphocytic infiltration and, at the end of 7 days, there was well-advanced macrophagic and fibroblastic-vascular activity.

This suggests that hypothermia induces a more rapid transition from the exudative to the reparative stage of the reaction to injury. It is inferred that hypothermia protects against the lethal effects of acute brain injury by modifying the posttraumatic inflammatory response.

The most important question raised by these investigations is yet unanswered: whether hypothermia is of value in the treatment of acute brain injuries when the injury has occurred at normal body temperature and when hypothermia is induced after variable delay periods. This study is now in progress, but results are too preliminary to report at this time.

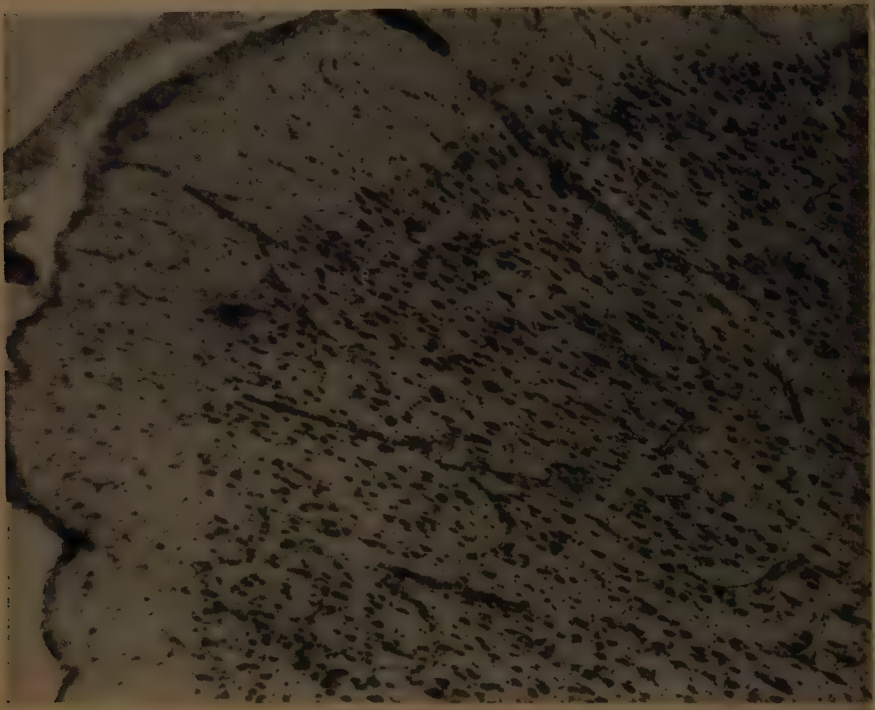

FIGURE 8. Microphotograph of the lesion, hypothermia, 12 hours after injury. Cresyl violet stain. Reproduced by permission from the *Journal of Neurosurgery*. × 15.

Concomitant with these laboratory studies, experience has been gained with the use of hypothermia in more than 100 patients. The methods of utilization have taken 2 forms. One has been the use of hypothermia as an adjunct in neurosurgical operative procedures; the other has been the treatment by temperature reduction of cerebral anoxia or severe brain damage due to other pathological processes.

Indications for the use of hypothermia for surgery at the Neurological Institute have been: (1) resection or ligation of vascular anomalies such as intracranial aneurysms and arteriovenous malformations; (2) removal of neoplasms that are either very vascular in nature or present with severely increased intracranial pressure; and (3) operations that require extraordinary exposure or that may compromise vital centers such as those about the optic chiasm, pituitary, third ventricle, and hypothalamus or brain stem. The temperature range utilized has been 26° to 28° C. At this level hypothermia induces a reduction in cerebral blood flow of more than 50 per cent, which facilitates hemostasis. Intracranial pressure is decreased 50 to 60 per cent and, in some instances, as shown by Lundberg and Nielsen,[7] the reduction may be as great as 94 per cent. This enhances operative exposure.

TABLE 1 lists the types of pathology encountered during surgery under hypothermia in the first 100 patients. One succumbed to ventricular fibrillation and cardiac arrest. We believe that this is a good record and is the result of the care taken to prevent reflexogenic cardiac arrhythmias.[8, 9] Sixty-one patients had vascular anomalies. Fifty-four of these were aneurysms; 7 were arteriovenous malformations. Four of the 7 malformations were removed successfully. Surgery of the 54 aneurysms was accomplished with an overall mortality rate of less than 25 per cent. Prior to the use of hypothermia, mortality of spontaneous subarachnoid bleeding from rupture of aneurysms of the circle of Willis was quoted as ranging between 35 and 50 per cent for the first bleeding episode.[10] One half of these patients died within 48 hours. Another 20 to 50 per cent of the survivors succumbed to recurrent hemorrhage.[11, 12] This was a total mortality rate of 50 to 75 per cent. Therefore, the reduction in mortality to less than 25 per cent is a considerable improvement, one that has been made possible by an aggressive approach utilizing hypothermia and early surgery. The surgery has been facilitated further by the use of a special clip technique.[13] This technique is one in which the artery to and from the aneurysm is occluded with special temporary clips, the aneurysm is dissected out and obliterated with a permanent clip, and then circulation is re-established in the main trunk artery with the removal of the temporary clips. It was not possible to accomplish this procedure at normal body temperature without risking the production of cerebral hypoxia. However, with the use of hypothermia the length of permissible occlusion is prolonged consequent to the reduction in metabolic needs, and this technique becomes practically feasible. In so far as tumor surgery is concerned, the data are too limited to support the drawing of conclusions. I agree with Sedzimir and Dundee that, technically, surgery is easier, due to the reduction in blood flow and brain volume, and that the postoperative course is more benign, particularly where operations have been performed in and about the third ventricle and the hypothalamus.[14]

TABLE 1

NEUROSURGICAL HYPOTHERMIA IN 100 PATIENTS

Vascular anomalies (aneurysms, malformations)	61
Neoplasms (such as meningiomas and gliomas)	22
Extraordinary exposure (sellar, III ventricular, CPA)	13
Miscellaneous	4
Total	100

TABLE 2

PROLONGED HYPOTHERMIA IN 30 PATIENTS

Cerebral edema (trauma, anoxia)	17
Subarachnoid hemorrhage and CVA	11
Cerebritis and encephalitis	2
Total	30

Prolonged hypothermia, up to three weeks in duration, has been used in the treatment of cerebral anoxia and other forms of severe brain damage (TABLE 2). The temperature has been maintained between 90 and 95° F. The evaluation of results of such therapy is extremely difficult. There is no good group of controls for comparison and each of these patients was close to or actually *in extremis* at the time of induction. Only impressions and

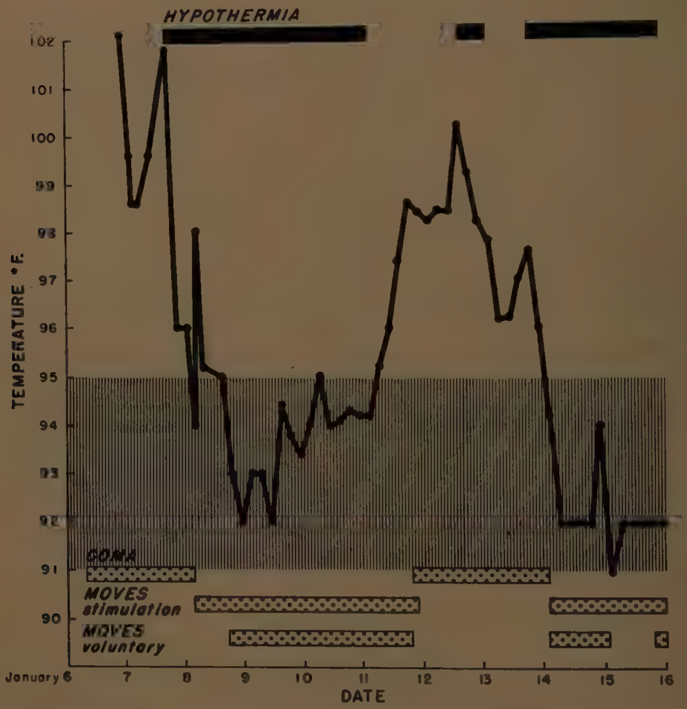

FIGURE 9. Effect of hypothermia upon the clinical status of a patient with a severely damaged brain.

interesting observations can be reported; one example is related in detail below.

This patient was a 27-year-old white female with a 3-year history of inter-mittent headaches (FIGURE 9). One month before admission she developed severe headache, nausea, vomiting, diplopia, and tonic seizures with deviation of the head and eyes to the right. Physical and neurological examinations were negative except for nuchal rigidity and generalized hyperreflexia. A lumbar puncture yielded bloody cerebrospinal fluid under a pressure of 340 mm. of water. Repeated bilateral carotid and vertebral angiograms were normal in appearance. Ventriculography disclosed a third ventricle mass with hydrocephalus. At surgery an angioma of the choroid plexus of the third and lateral ventricles was found and incompletely removed. The post-operative course was stormy and, following a generalized seizure, the patient became comatose and unresponsive. Hypothermia was induced and, as the body temperature fell below 95° F., she began to respond to painful stimulation. Shortly thereafter, it was possible to arouse her; she opened her eyes, followed movements, and attempted to talk. Four days later, she was allowed to rewarm, whereupon she became unresponsive and comatose again. Hypothermia was reinduced and once more she became responsive, awoke, and looked about. The papilledema that had developed prior to institution of hypothermia receded. This time hypothermia was maintained; however, 5 days later, she suddenly aspirated gastric contents, developed pneumonia, and died.

It has been the unanimous opinion of those who have utilized temperature reduction as a therapeutic agent in the treatment of the seriously ill patient that hypothermia has proved beneficial and, in some instances, lifesaving. Whether this be with the technique of artificial hibernation advocated by Laborit and his followers or with induction of hypothermia by other means, the results have been similar and depend on a single common denominator, a reduction of body temperature.[15-19] The mechanisms by which this is accomplished are not known but, in all likelihood, they relate to the effects of hypothermia on the normal and abnormal physiology discussed earlier in this presentation. It is hoped that, with continued research in both the laboratory and clinic, these mechanisms will be elucidated. Thereon will rest the eventual fate of hypothermia, either as an investigative tool or a therapeutic agent.

Acknowledgment

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HEAT TRANSFER FROM AND TO ANIMALS IN EXPERIMENTAL HYPOTHERMIA AND FREEZING

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The preservation of living cells and tissues in the frozen state at low temperatures is now a commonplace procedure. How small animals can be frozen for short periods at temperatures near the freezing point and then be reanimated successfully is also generally understood. The problem of storing a complete animal at a very low temperature at which prolonged arrest of vital processes would be possible is a great challenge, and some of our work has had this object in view. We realize that many readers may be less interested in these extreme exposures to cold than in the successful practice of surgical hypothermia. Nevertheless, from a physical viewpoint, the problem of removing heat from and restoring it to an animal is not greatly affected by the choice of the minimum temperature to be reached. We think that in our experiences of freezing and thawing small animals and of the various physical methods of transferring heat to and from them much will be found that is relevant to the immediate practical problem of attaining the hypothermic state in a large animal such as man.

Before discussing the problems of heat transfer we think it will be helpful to consider some of the physicochemical hazards faced by an animal at a body temperature lower than normal, because these hazards set the limits to the rates of cooling and rewarming consistent with survival. FIGURE 1 shows the time required for the cooling of isolated cells and tissue in a suspension occupying a volume of a few milliliters, and of various whole animals—the hamster, the rabbit, and man—when immersed in a cooling bath at about 0° C. Also shown are the times needed for cooling below 0° C. following immersion in a cooling bath at −140° C. The rates above 0° C. are from experimental measurements; those below 0° C. are calculated values with the exception of that shown for cells and tissue. In addition, FIGURE 1 gives the contours of two regions that illustrate the periods of time at various low temperatures inconsistent with survival of the cells and tissues or of the individual animals. The first of these regions is the small area close to the ordinate. This region, which begins at about 20° C., indicates the potentially harmful effect of cooling too rapidly. Some cells and tissues are sensitive to sudden cooling, and this phenomenon of thermal shock, which occurs well above and well below zero, must be borne in mind when rapid reduction of temperature is contemplated. The second and principal region indicates the harmful effects of cooling too slowly. As the temperature of an animal is decreased toward that at which its circulation and respiration cease, the survival time remains long compared with the usual duration of cooling. When breathing and heart beats cease, the survival time is greatly shortened but, as the temperature falls below this point toward the freezing point, there is some improvement, presumably because biochemical processes are slowed and oxygen requirements are diminished. Detrimental physical changes continue, but are reversible if the animal is rewarmed before its cells have become altered unduly. Below the freezing point there is a rapid decrease in survival time that is reduced to a few seconds for most living cells in the region of −30° to −40° C. Below this temperature the time of survival steadily lengthens until, at −80° C. and less, it may be prolonged indefinitely. During rewarming the same limitations are in force except that the region of thermal shock has vanished, for there is no indication of harm arising from sudden heating. The diagram illustrates that, even with small volumes of suspensions of

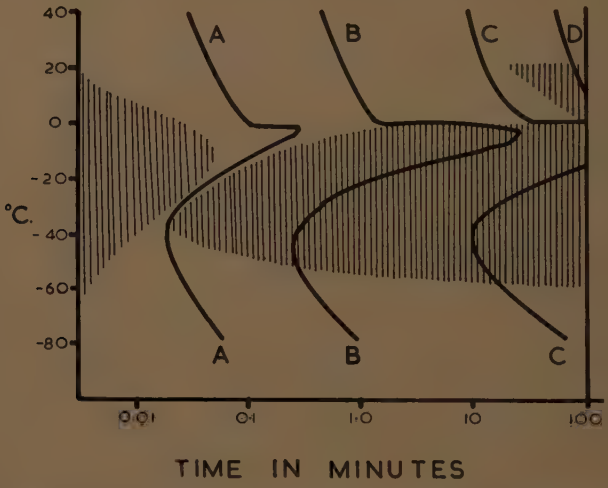

FIGURE 1. The times spent in cooling through one degree centigrade at temperatures between 40° C. and −80° C. The cooling (A) of a 1-ml. suspension of living cells, (B) of a hamster weighing 100 gm., (C) of a rabbit weighing 1 kg., and (D) of a man weighing 60 kg. The hatched regions indicate the times at the various temperatures in which irreversible damage occurs.

isolated living cells, it is difficult in the absence of glycerol to traverse the narrow corridor that permits survival in the region of −30° C. With small animals it obviously would be impossible to pass this zone safely. With large animals it would be difficult by external cooling even to reach 0° C. alive. The use of a protective agent, such as glycerol, helps to prolong survival of cells in the harmful regions below 0° C.; such an agent, however, rarely can abolish damage altogether.

Insofar as small experimental animals are concerned, cooling to temperatures at which the heart beat and respiration cease is a fairly straightforward technique based on the pioneering experiments of R. K. Andjus at Belgrade and Mill Hill. Briefly, the heat production of the animal is retarded by a combination of CO_2 anesthesia and partial anoxia while the animal is placed in an environment at approximately 2° C. As shown in FIGURE 1, the survival time in this region is long; man can be cooled sufficiently rapidly to permit short but therapeutically useful periods of circulatory arrest. When the circulation of the blood ceases either as a result of the lowered body temperature or from deliberate clamping of blood vessels to and from the heart, reanimation is possible only after a limited period. The duration of this period lengthens as the body temperature is reduced toward 0° C. Any increase in survival time gained at the lower temperature, however, always must have subtracted from it the time taken in passing from and to the temperature at which circulation ceased. Obviously, rapid cooling and rewarming are necessary if a useful prolongation of survival time is to be achieved. The physical problem is therefore largely a matter of removing and restoring heat at a rate appropriate to the physiological state of the animal and the temperature range concerned. Now let us consider the process of heat transfer and the ways in which this can be done.

Temperature is, of course, a measure of the average rate of molecular movement. The temperature of a body can be changed by either of two principal processes. First, if the molecules constituting the body are brought in contact with those of some other substances possessing a different temperature and average rate of movement, energy will be exchanged during collisions between the two sets of molecules until their average rates of movement are the same. This is the process which takes place when the animal is placed in a cold or warm bath of fluid. Such a process is slow because contact can occur only between the two sets of molecules at the surface of the animal and because it is hindered by the very structure of the integument, which is of such nature as to prevent any excess transfer of heat. For a given animal, the rate at which heat can be transferred must depend on the area of surface in contact with the hot or cold bath; the rate at which its temperature will change depends on the total inertia of its moving molecules. As the size of an animal is increased, its total heat capacity, which is related to its volume, grows faster than does the area of its surface; this is why the change of temperature of a large animal is slow. An extreme example of this effect is found in the whaling industry: when a dead whale is immersed in the freezing sea it cools so slowly that, unless those parts which are of economic importance are dissected out rapidly, serious decomposition can occur in them. By contrast, the hummingbird, which weighs only a few grams, loses heat to the environment so rapidly that when at rest it can maintain a temperature in the region of 37° C. for only short periods; when resting for a longer period, it is forced to hibernate. The second principal way by which moving molecules can lose or gain energy is radiation: a vibrating or rotating molecule can emit electromagnetic radiation and thereby lose energy of motion. Similarly, it can receive radiant energy and be set in motion. The radiant energy emitted by the molecules of an animal at its normal temperature is in the far infrared region; the animal's tissues are opaque to this radiation, so that the emission of radiant energy by molecules in the interior of an animal serves only to exchange energy with those in its immediate vicinity. Cooling by radiation can occur only from the surface and this, like cooling by conduction, is a slow process. Heating by radiation is quite different. If radiation to which the animal is partially transparent is chosen, it is then possible to induce motion simultaneously in molecules throughout the animal. The limitations of surface heating no longer apply, and this forms the basis of the successful methods of rewarming that will be discussed later.

Methods of Cooling

Surface cooling in baths. An animal corresponds physically to a bag made of heat-insulating material filled with a viscous fluid that may or may not be stirred, depending on whether the blood is circulating. FIGURE 2 shows the similarity of cooling curves obtained from an artificial hamster (made of a polythene bag containing 100 ml. of saline and covered with hamster fur) and from the intact animal when both were immersed in baths at −5° C. While cooling such a vessel, most of the temperature gradient will be found in the insulating layer that corresponds to the skin and subcutaneous tissue. This is illustrated in FIGURE 3, which shows the temperature distribution in a hamster immersed in a bath at −5° C. The greater part of the interior of the trunk is seen to cool at more or less the same rate and the principal temperature gradient is in the skin and subcutaneous tissue. With an animal of spidery shape, the galago, for example, the rate of cooling of the long slender limbs and tail will be faster than that of the body; survival, however, is probably determined by the cooling of the trunk. In mammals as large as the dog remarkable differences in the temperatures of different internal organs

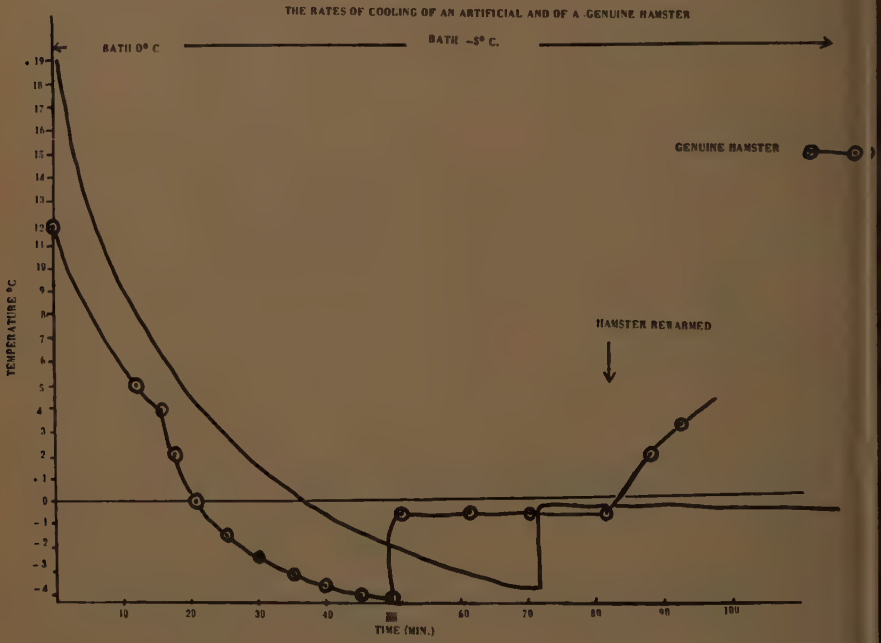

FIGURE 2. Records of the fall in temperature of a hamster (o——o), and of a polythene bag covered with hamster fur and containing 100 ml. of water (——) during immersion in melting ice and then in a bath at −5° C.

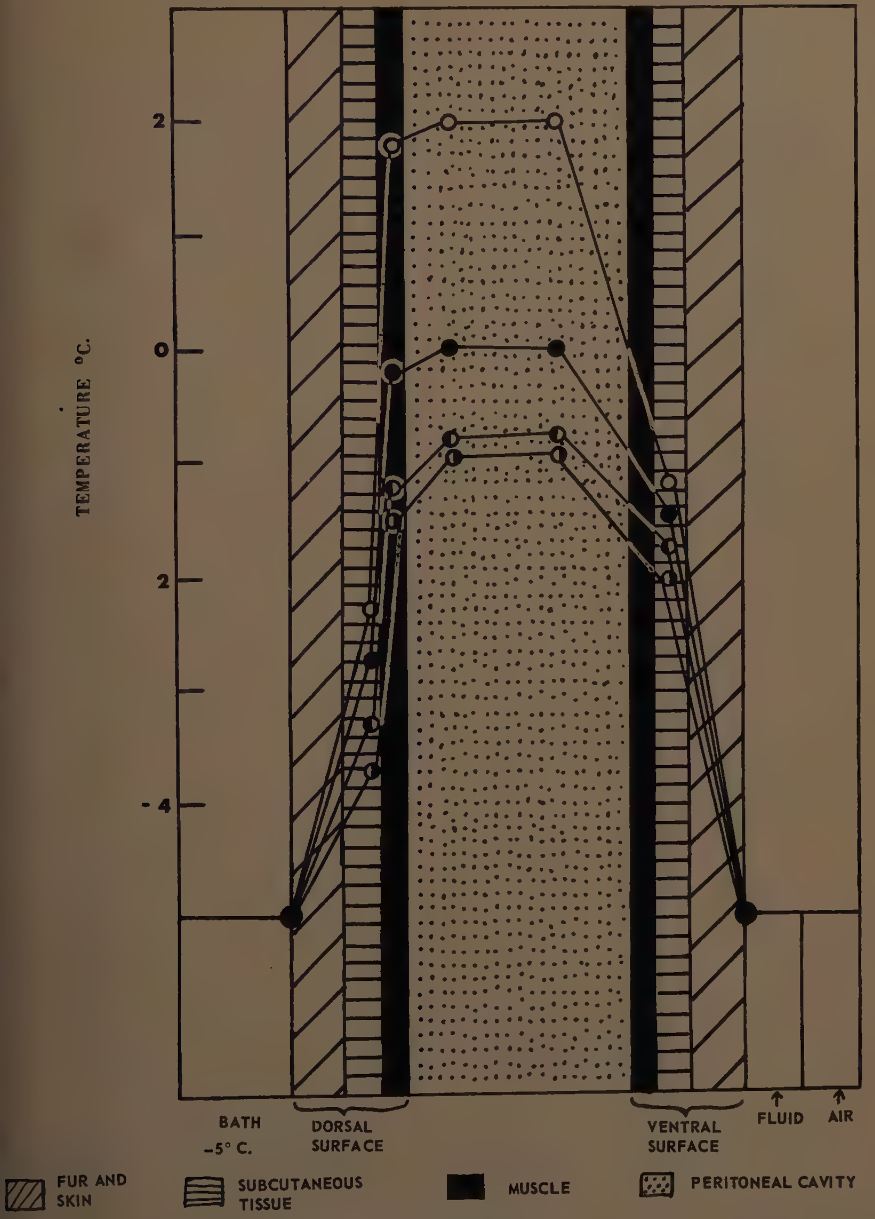

FIGURE 3. The distribution of temperature within a hamster during cooling in a bath at −5° C. Reproduced by permission from *The Proceedings of the Royal Society*.

have been recorded during cooling in baths. These differences are still small in comparison with the gradient through the skin.

The rate of cooling of an animal is determined principally by its surface-to-volume ratio; however, the thickness of the skin and hair, and whether the cooling bath is stirred, all have some influence on the cooling rate. This is illustrated in FIGURE 4, which shows the rates of cooling of a hamster in

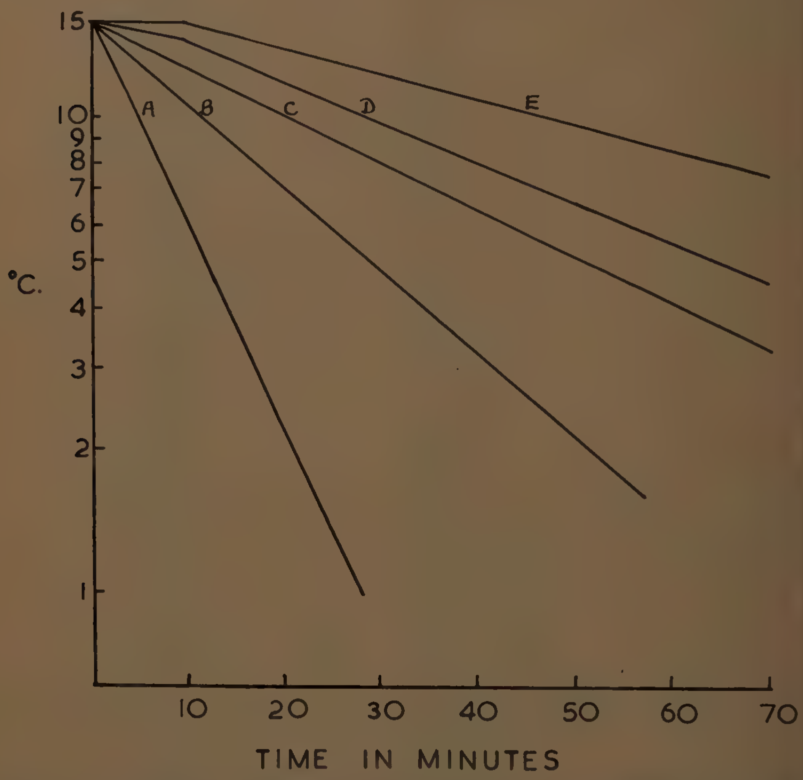

FIGURE 4. The rates of cooling in a bath at −5° C. of: (A) a hamster, (B) the shaved corpse of a dead rabbit, (C) a dead rabbit unshaven, (D) a live rabbit with its abdomen shaved, and (E) a live rabbit.

comparison with those of a rabbit: alive, dead, and with some or all of its hair shaved off. The rabbit is seen to cool much more slowly than the hamster, although the removal of hair considerably increases the cooling rate. The rate of cooling of the same rabbit, alive or dead, was not very different, which suggests that in the region of 15° to 10° C. heat generation by metabolism does not hinder greatly the process of cooling. These results, however, do emphasize the unsuitability of cooling larger animals by immersion in baths when the body temperature is to be reduced below 15° C. because of the long period spent at intermediate temperatures after heart beats stop.

Cooling by the circulation of cold fluid. One method of overcoming the limitations of heat transfer through the skin is to connect an external cooling loop to the blood vessels of the animal. This method has been developed to the status of a highly successful technique by Gollan and his co-workers (1955) and by other groups of workers in the United States, Great Britain, and elsewhere. Clearly, from a physical viewpoint there is no difficulty in cooling to its freezing point (−0.5° C.) the blood contained in an external loop. Provided it has not been frozen solid, it can be returned to the animal. The rate of heat transfer from the animal would depend on the proportion of its blood passing through the external circuit. As the temperature falls and the circulation slows, it is necessary to maintain the blood flow by external pumping. Ross (1954) used a loop of 50-ml. capacity in dogs so that the blood pressure was not reduced by excessive loss of blood from the systemic circulation. The refrigerant surrounding the coil was at −5° C. The deep body temperature fell at the rate of 1° C. in 5 min. It easily could have been reduced more rapidly. It would be interesting to learn from Gollan the maximum rate of cooling that can be obtained and be used safely. When the blood is cooled in an external circuit the simultaneous use of a bath to cool the surface of the body is likely to be of value only with the smaller animals. With an animal as large as man, the rate of cooling made possible by using an external circuit of blood is so much greater than the maximum rate obtained by cooling the surface of the body that immersion in a cold bath is almost certainly a superfluous complication.

Other possible methods such as washing out the various body cavities by cooling fluids are intermediate between cooling by baths and by an external circulation. Where lavage is contemplated, the use of a slurry of ice crystals in a medium such as serum greatly increases the efficiency of the method. Ten per cent of ice in serum, for example, has 8 times the cooling capacity of serum alone at 0° C.

Cooling below 0° *C.* After the blood has frozen it is obviously impossible to cool the circulation. Lavage of bodily cavities with some inert material such as silicone, however, may be possible. On the other hand, there are several factors that would render surface cooling more favorable for the purpose of cooling the whole body at temperatures below its freezing point than at temperatures above 0° C.

Once ice has formed in the skin of the animal the rate of heat transfer increases considerably. This is illustrated in FIGURE 5, which shows the rates of heat loss from hamsters in a bath at −5° C. before and after the onset of freezing. This increase in the rate of heat loss is due to the fact that heat transfer through ice is ten times more rapid than through water.

Cooling to temperatures many degrees below 0° C. is not likely to be attempted until a satisfactory technique has been developed for treating the whole animal with some protective agent, such as glycerol. The presence of a protective agent in the blood and tissue fluids would permit relatively slow cooling in the lower temperature ranges, and surface cooling would meet the requirements. Finally, glycerol-treated animals theoretically could be immersed in baths at temperatures as low as, or below, −80° C. without danger of damaging the skin or inducing frostbite. This would increase considerably the rate of heat loss. In spite of these potentially favorable influences, which may increase the rate of heat transfer ten times or more, the rate of fall of temperature in the freezing region is very slow. This reduction in the rate of fall of temperature is caused by the great quantities of heat released by the water in the body of the animal as it freezes. In the absence of some protective agent, this factor alone would render the freezing of an animal to very low temperatures incompatible with its survival.

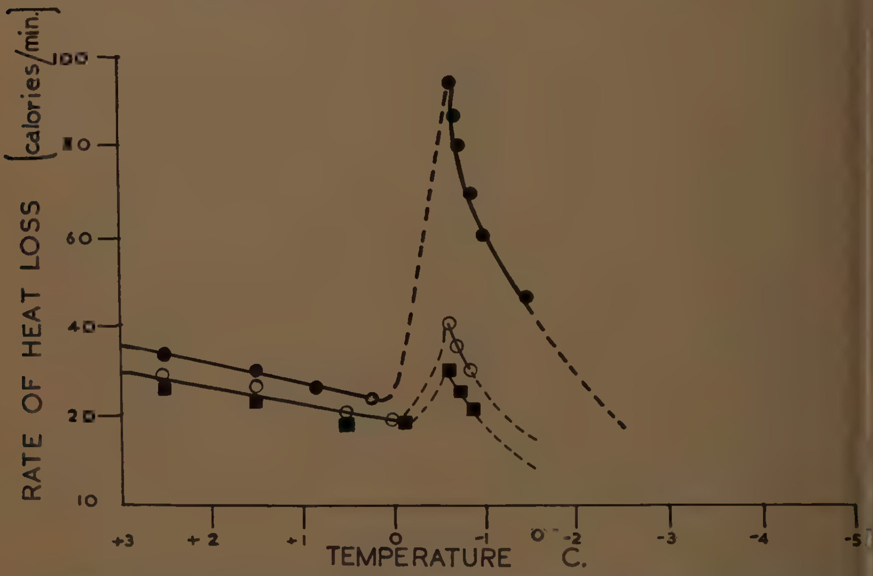

FIGURE 5. The rate of heat transfer through the skin of hamsters before, during, and after the onset of freezing. Reproduced by permission from *The Proceedings of the Royal Society.*

The problems of permeating an animal with some protective agent such as glycerol before freezing, and of removing the agent after thawing, are formidable. If, however, this could be done there is a slight chance that the animal could survive freezing to and from temperatures as low as −80° C. All of the experience with isolated cells and tissues suggests that a glycerol-treated animal that had been successfully cooled to this temperature would contain many potentially viable cells. There is evidence of survival in isolated organs frozen in this way. There seems no inherent reason why the various organs and systems should not resume concerted action when thawed. We are aware, however, that undue optimism usually stems from ignorance.

Rewarming

In baths of warm fluid. At all temperatures from the lowest upward, surface rewarming has undesirable features. With an animal in the frozen state the warm bath would first thaw the skin; as soon as an appreciable layer of the skin had thawed, the rate of heat transfer would fall to one tenth its initial value. This, of course, is due to the slow rate of heat transfer through water as compared with ice. A well-known example of this effect is the feat of cooking, in which ice cream is successfully baked in beaten egg white.

Above 0° C. it is possible to warm the interior of the body by heating the surface as fast as the interior can be cooled by refrigerating the surface. However, we have already seen that such a rate might be too slow because of the prolonged period that might be spent in a biologically dangerous temperature range. Even if it were not too slow, surface heating might be risky for physiological reasons and may be incompatible with revival of severely chilled mammals. For example, the capillaries and blood vessels near the surface would tend to dilate so that the peripheral resistance would be at a minimum and the pressure of blood circulating to vital organs would be inadequate. Behnke and Yaglou (1950) showed that the internal temperature of a hypothermic subject actually fell after immersion in a warm bath, presumably because a large volume of cold blood from the skin suddenly returned to the heart and internal organs. The condition of the subject then deteriorated.

Rewarming by radiation. In this region above 0° C., warming by recirculating blood heated in an external circuit is an effective method, but rewarming by radiation is probably to be preferred. It would be possible to warm an animal with X rays, but such a technique would hardly be compatible with its reanimation. In the near-infrared region the depth of penetration is only a few millimeters; nevertheless, this type of radiation has been successfully used in the rewarming of small animals (Goldzveig and Smith, 1956; Smith, 1957). The most useful region, however, is among the radio frequencies. Above a wave length of 10 cm. the depth of penetration increases from 7 mm. to 100 cm. at a wavelength of 30 m. At the longer wave lengths the depth of penetration is sufficient to warm a man uniformly.

With the shorter wave lengths of about 10 cm. the animal can be rewarmed simply by submitting it to a beam of the radiation (Andjus and Lovelock, 1955). At these frequencies the depth of penetration is, however, too slight for the method to be of use with any but the smaller animals. At the lower and more useful frequencies, radiation sources become so large compared with the dimensions of the animals that it is impracticable to use on them a beam of sufficient intensity for useful heating. Fortunately, radiofrequency radiation can be applied directly to an animal by either of the following methods, and at intensities amply sufficient for rapid rewarming.

(1) *Dielectric heating.* In this method the animal is placed in an alternating electric field that is one isolated component of the radiation. The electrically charged molecules of the animal, a high proportion of which are water molecules, move following the alternations of the electric field. During these movements they collide with other molecules and, when they do so, their rhythmic alternating motion is converted to simple random motion, which is, of course, heat. The apparatus required for this method has been described (Lovelock and Smith, 1956). It consists briefly of two metal plates

connected to a source of radiofrequency energy. The area and distance between the plates are determined partly by the size and shape of the animal, the greater part of which must be enclosed within the air space between the plates, and partly by the frequency of the radiation used. For the frozen

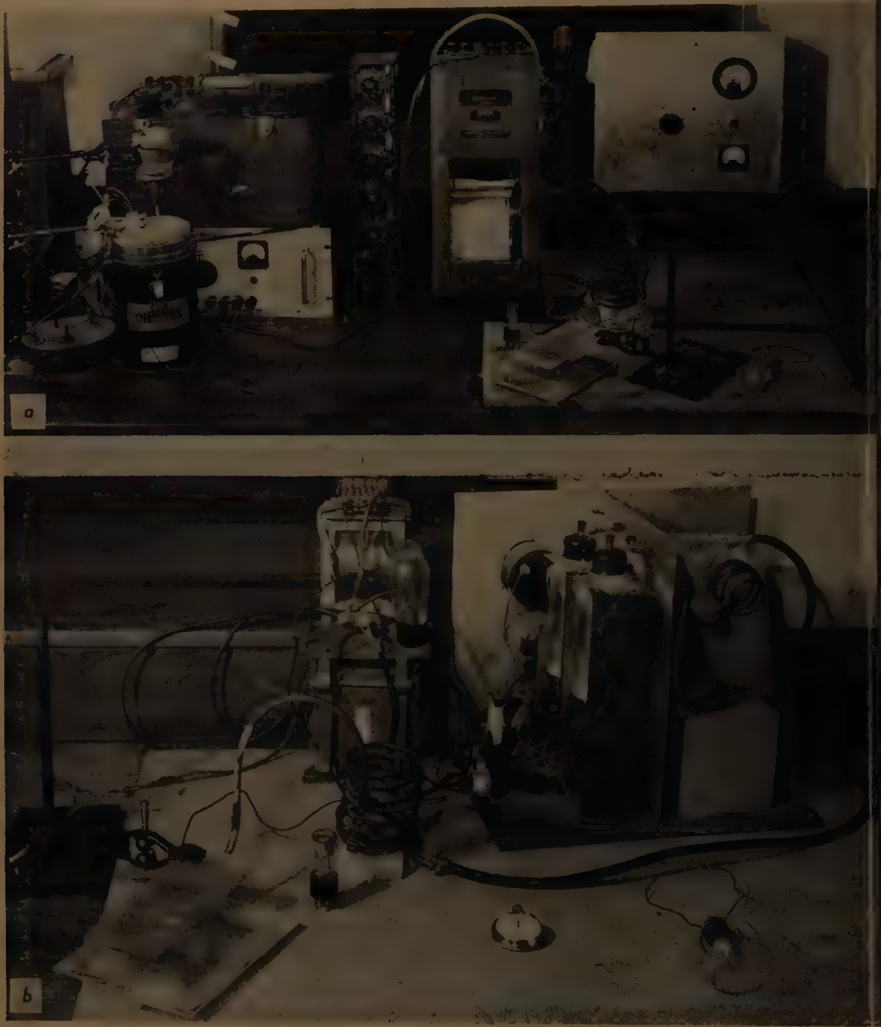

FIGURE 6. Apparatus for rewarming frozen hamsters (and other animals of approximately 100-gm. body weight) by dielectric heating. (*a*) Front view; (*b*) back view.

hamster, a power input to the plates of 120 w. was used. The wave length of the radiofrequency energy was approximately 10 m. (that is, a frequency of 27 Mc./sec.). No attempts were made to measure the applied potential of the alternating field, but conditions were arranged experimentally to favor the maximum transfer of energy to each individual animal. In general terms, the higher the frequency, the smaller the area of the plates that can be used, but the greater the intensity of the power that can be applied to the animal. For these reasons the method is best suited to rewarming small animals of compact shape. With large or long-limbed animals it is difficult to maintain a sufficiently high intensity for rapid heating and a sufficiently uniform electric field for uniform heating. With this reservation, the method is excellent for thawing and rewarming small animals. It is simple to use.

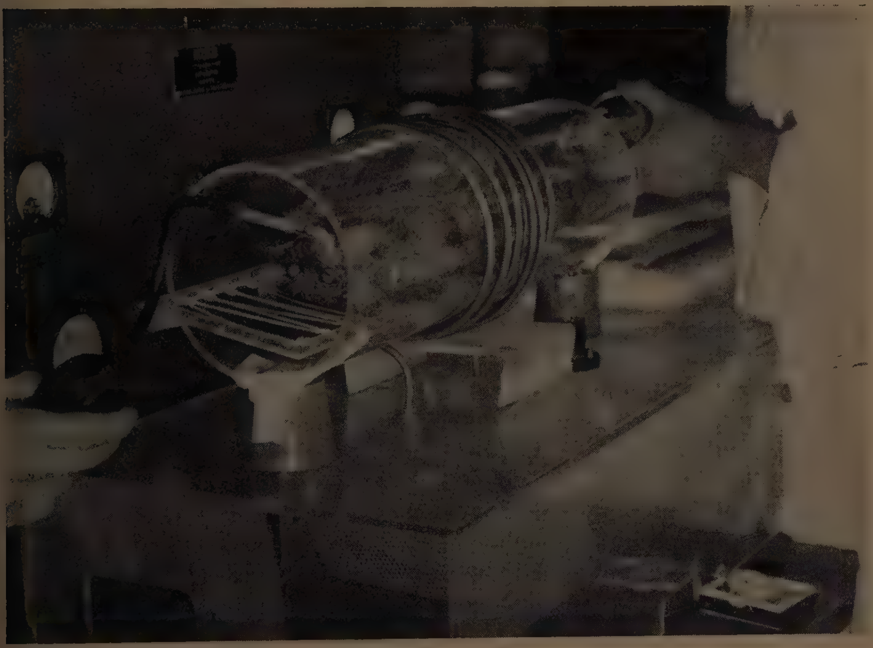

FIGURE 7. Apparatus for rewarming animals up to 1-kg. body weight by induction heating. Reproduced by permission from *The Proceedings of the Royal Society.*

The apparatus we used in thawing and rewarming frozen hamsters is illustrated in FIGURE 6*a* and *b*.

(2) *Induction heating.* In this method the animal is placed in an alternating magnetic field which is the other component of electromagnetic radiation. The body fluids of the animal are good conductors of electricity and the alternating field induces in them circulating currents that warm the animal just as would any electric current. At these high frequencies, currents in the region of many amperes can be produced within the animal without any effect other than heating and without risk of death from electrocution. The apparatus for this method also has been described (Lovelock, 1957); a photograph of it is shown in FIGURE 7. It consists of a helical coil of stout copper tubing of sufficient size to enclose the animal. This coil is connected to an alternating supply of high-frequency energy. With this

method high power inputs can be applied to coils large enough to enclose any animal. Heat is uniformly distributed within the animal and we have found it possible to warm a rabbit at a rate of 16° C./min. from 0° C. to 20° C. without obviously overheating or harming the structure of any part of the animal. Frequencies in the region 10 to 30 Mc./sec. are suitable for induction heating. The larger the animal, the lower the frequency that should be used because, briefly, the shorter the wave length, the smaller the apparatus required.

General Comments on Radiation Heating

Thawing frozen animals. Whatever method of radiofrequency heating is used to thaw a frozen animal—both dielectric and induction heating are effective—heat is generated not in the ice but in the small volume of water remaining unfrozen in the interstices between the ice crystals. This is because ice has a low dielectric constant compared with that of water and is a poor conductor of electricity. This factor is helpful in thawing the frozen animal, since it ensures that heat is liberated first in the cells of the animal or in their immediate neighborhood. It would assist in warming them rapidly through dangerous temperatures of or near −40° C., as well as at their freezing point. It is also helpful in temperatures above 0° C., since the animal can be packed in ice during the course of induction heating. There are grounds for believing that it is desirable to keep the skin cool during the early stages of rewarming from 0° C., perhaps to keep the superficial blood vessels constricted.

The maximum possible rate of heat input with radiation heating is very high. Isolated suspensions of 1 ml. of red blood cells have been thawed from −80° C. in 1 sec. without harm. This corresponds to a heat input of 200 w./cc. There is no reason to believe that radiofrequency energy has any effect other than heating on the cold animal. At normal body temperatures, 37° to 40° C., there are, however, certain dangers in the use of radiation heating. Some tissues, the lens of the eye and the testes in particular, are sensitive to overheating and are at sites where, because of exposure or poor blood supply, an excessive temperature rise can occur easily. At normal body temperatures a flux of 10-cm. radiation of only 0.1 w./sq. cm. can irreversibly damage the lens of the eye in the course of a few minutes. At body temperature of 20° C. a local rise in temperature of 5° C. would be immaterial.

Another method of radiofrequency heating is to enclose the animal within a metal cavity resonant at some convenient frequency. This method is effective, but would appear to have no special advantage over induction heating. One other method of radiation heating is the use of ultrasonic radiation. This method is also quite effective and might have certain advantages in experimental work requiring measurement by thermocouples of the temperature of the various parts of the animal during rewarming. With radiofrequency heating this is a difficult matter because of the disturbances of the radiation field by the metal of the thermocouple.

We may say, in conclusion, that physical methods are now available for thawing and rewarming small and comparatively large mammals. These methods are well established, and the limits of the problem are set by the biological requirements of the animal rather than by those of the apparatus. The techniques for cooling and, particularly, for freezing are not nearly so far developed. For example, if it were possible to reduce the body temperature of a man to 0° C. or to just below 0° C. as rapidly as the temperatures of a hamster or a rat can be reduced in this range, it seems probable that reanimation would be feasible. Many experiences with the isolated cells and tissues of man indicate that their resistance to cold and to freezing is higher than the resistance of cells and tissues from the rodents. Further improvements in cooling technique will almost certainly come from the work of Gollan and others on the exchange of hot blood for cold. There is little chance that some recondite physical process, the converse of diathermy, will be discovered despite the variety of cooling rays suggested in science fiction.

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THERMOGENIC FACTORS DURING COOLING AND IN THE STABILIZED HYPOTHERMIC STATE

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Introduction

Thermogenic factors in cooling may be divided into two broad categories: those arising from shivering, and those arising from sources other than shivering. In 1872 Bernard[1] proposed that there exists a nonshivering source of heat production in addition to shivering. Subsequent failure to demonstrate its presence led physiologists generally to disbelieve its existence; even the support to this theory lent by Rübner,[2] Lefevre,[3] Cannon *et al.*,[4] and others failed to change the final decision; therefore, between approximately 1900 and 1954, shivering was considered the only active mechanism of thermogenesis in the cold. In 1955 Davis and Mayer published results that they interpreted as measuring the metabolic contribution of shivering and nonshivering heat production.[5] In the year before, Sellers *et al.*[6] demonstrated that in spite of a high oxygen consumption in the cold, the cold-acclimated rat shivered less than the unacclimated rat. More recently, Heroux, *et al.*,[7] Cottle and Carlson,[8] and Davis *et al.*[9] substantiated his findings.

The contribution of shivering as a thermogenic factor has never been in doubt. The cold and warm perfusion experiments and the recent hypothalamus heating experiments of Hardy *et al.*[10] demonstrate that heating of the hypothalamus inhibits shivering while its cooling causes stimulation. The development by Keller of the poikilothermic dog by selective ablation of the hypothalamus again demonstrates the importance of this region in the regulation of shivering.[11] However, in the intact preparation, peripheral stimulation of shivering via skin receptors appears to be of the greatest importance and, in the present state of our knowledge, the question of how the hypothalamus and peripheral receptors cooperate to regulate shivering remains a puzzling one.[12]

Shivering appears to be a mercurial mechanism subject to the influence of factors such as psychical stimulation, oxygen tension, time of day, and seasonal change. The most concrete modifier of shivering in both animals and man appears to be prolonged exposure to cold.

Shivering Activity and Its Relationship to Skin Temperature

In these experiments shivering activity was measured by integrating the electromyographically amplified muscle action potentials. Skin and colonic temperatures were measured by thermocouples.

FIGURE 1 shows the relationship between the development of shivering activity, colonic temperature, body skin temperature, and tail skin temperature in shaved rats exposed to 5° C. air temperature. Shivering activity is expressed as units per minute. Temperatures are in degrees centigrade.

The abscissa is exposure time in minutes. The rise in shivering activity shown in the top curve may be seen to be a mirror image of the fall in tail skin temperature measured at the root of the tail distal to the end of the hairline. A negative correlation between the rising shivering activity and the falling tail skin temperature of better than 0.9 was obtained. Correlations with colonic temperature and body skin temperatures were 0.03 and 0.34, respectively.[13]

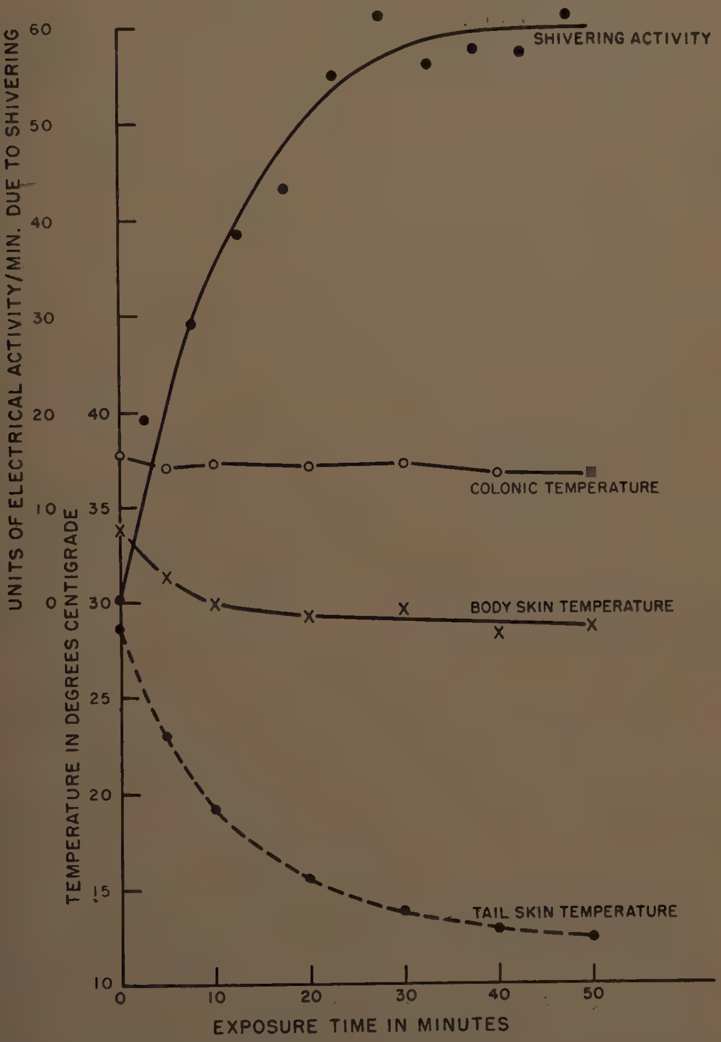

Figure 1. Curves of body temperatures, skin temperatures, and shivering activity in shaved rats exposed to cold (5° C.).

Figure 2 demonstrates the effect of insulation upon the development of shivering in rats. Each point on the 3 curves represents observations on 10 animals. The top curve is the rising shivering activity recorded from shaved animals. The middle curve is shivering activity recorded from unshaved animals, and the bottom curve is shivering activity recorded from unshaved animals with tails insulated with absorbent cotton. A significant difference in the shivering levels at the end of 50 min. of exposure to an air temperature of 5° C. was obtained at the 1 per cent level of confidence.[13]

FIGURE 3 shows findings in man as a result of immersion in sea water at a temperature of 11° C. Six observations were made, but the different conditions encountered in each preclude grouping the data. This observation is presented as representative of what was found in each case.[13] The top curve is rectal temperature, the middle curve is an estimate of skin temperature, and the lowest curve is shivering activity obtained by subjective observation. The abscissa is time in minutes consisting of, from left to right, the period of immersion, a dressing period, a period of walking, and a period of resting quietly in a warm room. During the period of immersion the rectal temperature is seen to rise sharply from a control temperature of 37.4° C. to 39.2° C. This is followed by a fall to 38.3° C. where it remains until the postimmersion period. During the immersion period, skin temperature is estimated as having fallen to near water-temperature levels. Also during this period violent shivering was observed. Thus shivering was occurring when core temperature was high and skin temperature was low. During the postimmersion period core temperature fell precipitously, taking about

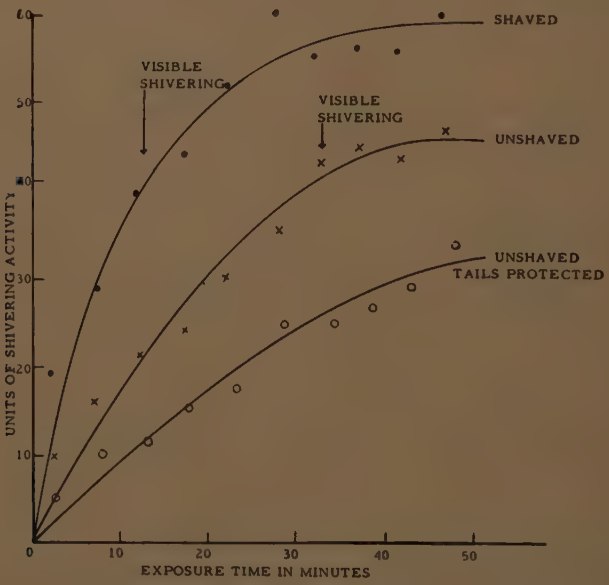

FIGURE 2. Curves of shivering activity in the cold (5° C.) in rats (10 animals) shaved, unshaved, and unshaved with tails protected.

2 hours to return to the pre-experimental level. Shivering during this period was not demonstrable and skin temperature was estimated as having risen to near the pre-experimental level. Thus shivering was absent during a state of mild hypothermia, while skin temperature had risen to the pre-experimental level.

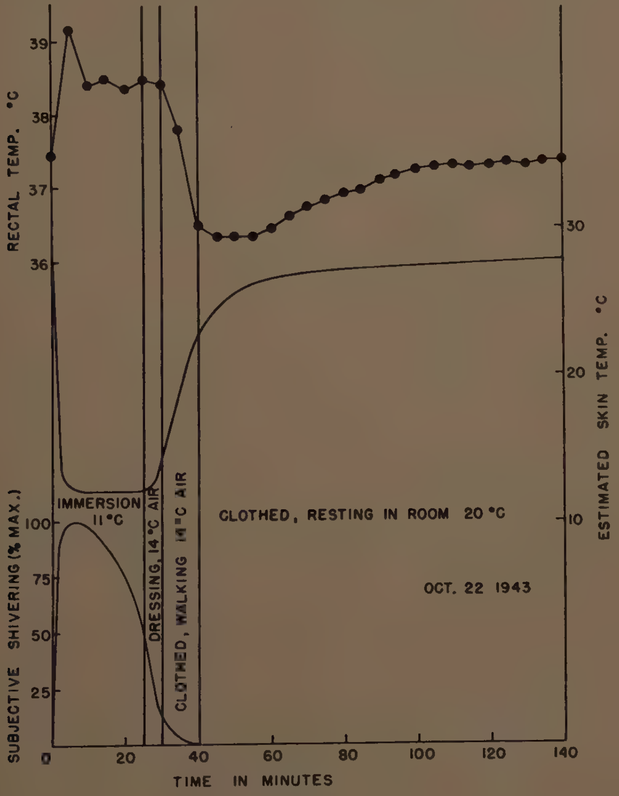

FIGURE 3

Under the conditions of these experiments it may be concluded that under normal conditions of cooling, shivering is stimulated by a fall in skin temperature, and that the thermal state of the center appears to play no major role in either inhibiting or stimulating shivering.[13, 14]

Shivering and Its Relationship to Central Temperature

Barbour has demonstrated that cool and warm perfusion of the brain would invariably stimulate and inhibit shivering, respectively.[15] More recently Hardy has been able to implant electrodes in the region of the hypothalamus. These electrodes can be heated in the otherwise intact and conscious animal. Heating the electrodes while the animal is in a thermoneutral environment causes panting which, in turn, causes a fall in core temperature. Almost immediately after heating is discontinued, the dog exhibits typical shivering, presumably as a result of the lowered central temperature.[10]

In Keller's poikilothermic preparation of the hypothalamus in dogs,[11] hypothermia occurs as a result of a deficit in thermogenesis and, even though the central temperature is below 30° C., no shivering is in evidence at any time, indicating the importance of an intact central nervous system for the induction of shivering. Uprus has demonstrated adequately the dependency of shivering upon an intact efferent pathway in man.[16]

Our own experiments using diathermy substantiate the fact that the thermal state of the core does influence shivering.[13] Essentially, this series of experiments attempted to evaluate the relationship between shivering and combinations of core temperature and skin temperature in the conscious and intact animal. On the basis of the data obtained in mice it was concluded that between core temperature of 34° and 40° C. shivering could be demonstrated providing skin temperatures were low, and that shivering could be inhibited at any time by raising skin temperature. If, on the other hand, core temperatures were raised above 40° C. by the application of high diathermic intensities, shivering was inhibited and this inhibition was accompanied by a reflex peripheral vasodilatation which, despite the continued application of diathermy, increased heat loss and lowered central temperature. Below a core temperature of 34° C. shivering could not be inhibited even though skin temperature was raised to 40° C. Therefore, it was concluded that, with core temperatures between 34° and 40° C., shivering was primarily both stimulated and inhibited by skin temperature changes. Above 40° C. shivering was inhibited by the need of the animal to lose heat by vasodilatation. Below a core temperature of 34° C., since shivering could not be inhibited by raising skin temperature, it probably was being stimulated by the low core temperature.

These experiments indicate that shivering thermogenesis may depend upon peripheral receptors in the skin, as demonstrated anatomically by Hensel,[17] as well as upon central receptors in the hypothalamus. Another possibility exists in the suggestion that the hypothalamus is the receiving center of stimuli from peripheral receptors, and that the degree of shivering is dependent upon the thermal state of the hypothalamus. This possibility is not in harmony with the fact that a low hypothalamic temperature can stimulate shivering in the presence of a high peripheral temperature, as demonstrated by Hardy *et al.*[10]

A third possibility is that shivering is dependent upon changes in total body heat content via receptors in the hypothalamus, in the skin, and also, perhaps, in areas intermediate between the skin and the hypothalamus. Especially may this be so in that the quantity of shivering is maintained in a cyclic manner with periods of activity separated by periods of quiescence, as illustrated in FIGURE 4.

This figure depicts the development of shivering in 9 nude human subjects during an exposure to 14° C. air temperature for a period of 60 to 70 min. It illustrates a variability of time of onset of shivering from 4 to 55 min. It also illustrates the degree of variability in the amount of shivering in each individual at any one moment during the period of exposure, and likewise illustrates the cycling or periodic character of shivering activity. The periodicity of these cycles appears to remain fairly constant for an individual, ranging in these 9 subjects from a minimum time of 15 min. to a maximum of 45 min., measured between peaks. In these subjects no changes in rectal or skin temperatures could be correlated with the periods of shivering activity and inactivity. However, the crudeness of rectal temperature as a measure of changes in central temperature is well known. A rise of temperature of vena cava blood in the dog, however, correlates to some degree with bursts of shivering. Therefore, it is reasonable to postulate, as a working hypothesis, that shivering in the normothermic animal is stimulated fundamentally by the falling skin temperature, but that its quantitative regulation may be dependent upon changes in core temperature. In the truly hypothermic homeotherm, however, shivering appears to be stimulated entirely by the low central temperature.

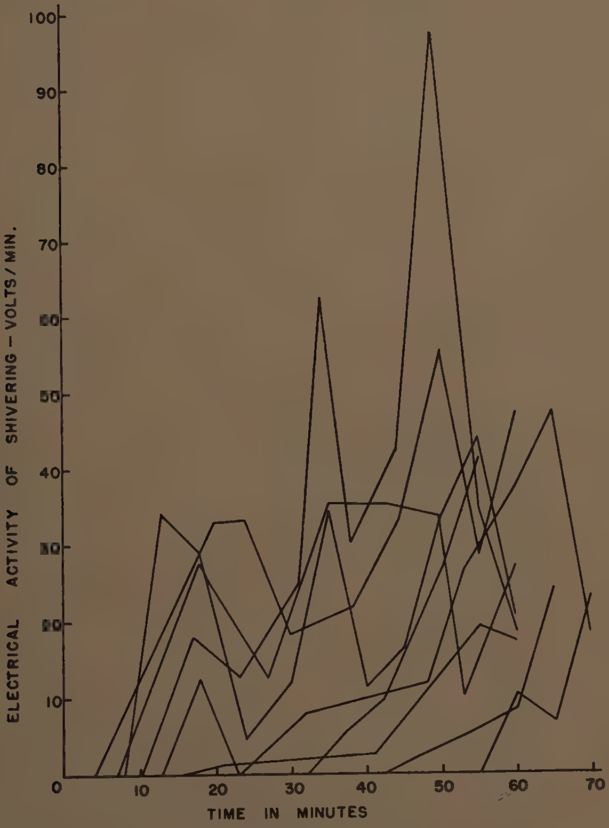

Figure 4

Evidence of Nonshivering Sources of Heat Production

In the unacclimatized animal Davis and Mayer,[5] using the techniques of curarization and diathermy, interpreted their results as quantitatively demonstrating the relative metabolic contributions of shivering and nonshivering thermogenesis in the cold. The nonshivering poikilothermic preparation of Keller in the unacclimatized dog shows evidence of nonshivering heat production in that the dog is able to rewarm if the environmental temperature is not too much lower than core temperature.[11]

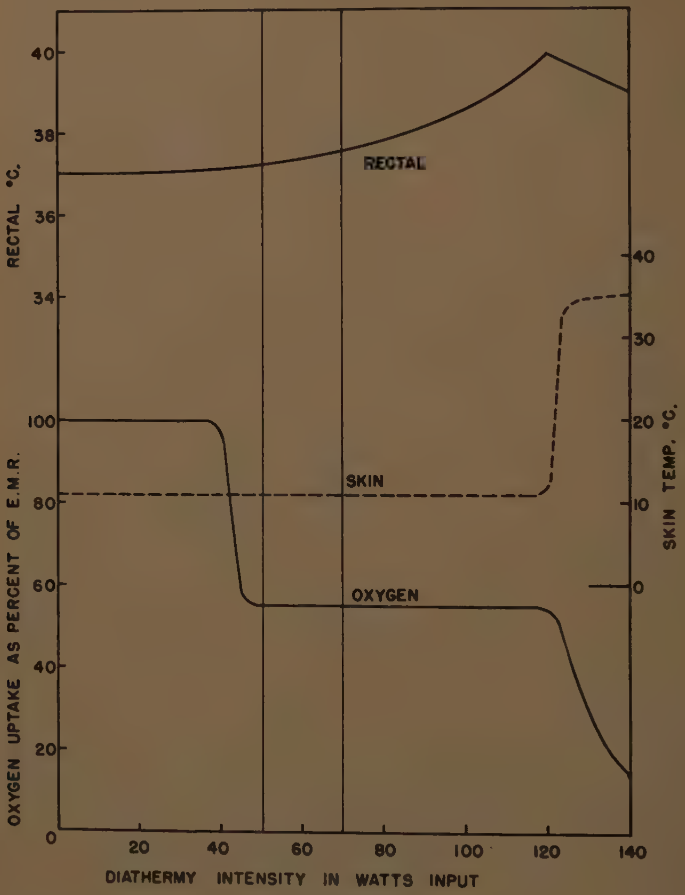

FIGURE 5

FIGURE 5 shows, from top to bottom, the response curves of rectal temperature, skin temperature, and oxygen consumption as a function of diathermy intensity administered for a duration of 10 min. at 10-w. increments in rats fully stabilized to an air temperature of 5° C. The diathermy current was at a frequency of 27.12 Mc. Rectal and skin temperatures are in °C., while oxygen consumption is expressed as a percentage of the cold-induced oxygen consumption or environmental metabolic rate (EMR). BMR is therefore zero per cent. As the intensity of diathermy increases, rectal temperature rises without, however, an accompanying rise in skin temperature. At an intensity of 120-w. input to the final stage of the diathermic wave generator, the rectal temperature at the end of diathermy is about 40° C., while the skin temperature rises sharply, indicating an active vasodilatation. Continued application of diathermy after vasodilatation takes place does not produce a further increase in rectal temperature, presumably because the heat loss effected by vasodilatation is greater than the heat generated not only by the diathermy, but also by the animal. Oxygen consumption responds to the increasing diathermic intensity by remaining at the initial level until an intensity of about 40 w. is reached, whereupon it falls to a level of 56 per cent of the initial value. It remains at this new level until an intensity of 120 w. is reached, where it shows a tendency to fall. The lowered level of oxygen consumption occurring between 40 and 120 w. is interpreted as resulting from a raised central temperature; its failure to fall further as a function of increased diathermic intensity was interpreted as resulting from the continued stimulation of the low skin temperature.[9] Thus, the suggestion of Richet[18] that cold-induced metabolism consists of a centrally and a periph-

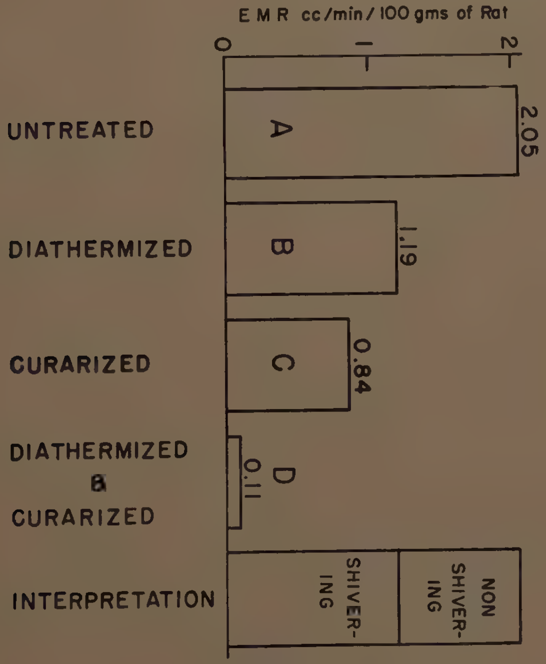

Figure 6

erally stimulated fraction appears to have been demonstrated. The role of shivering and its relation to these two fractions was demonstrated by the experiment depicted in FIGURE 6, in which curare was used, as well as diathermy at intensity levels that produced oxygen consumption depression without affecting skin temperature.[5]

The criteria for curare dosage were as follows: (1) the effect of curare lasts for 8 to 10 min.; (2) body temperature and metabolism are the same before and after curarization; (3) the muscles are paralyzed, as indicated by muscular collapse; and (4) the animal survives the treatment.

The ordinate is cold-induced oxygen consumption or environmental metabolic rate (EMR) expressed as cc./min./100 gm. of rat. The various conditions of the experiment are given below each bar graph. Bar graph *A* represents cold-induced metabolism in untreated animals. *B* is the metabolism of the rats exposed to cold and irradiated with diathermy. *C* is the metabolism of cold-exposed rats treated with curare, and *D* is the cold-induced metabolism of animals treated with curare and irradiated with diathermy. The last bar graph is the interpretation of the results.

By interpretation of the effect of diathermy,

$$A - B = \text{metabolism stimulated by central temperature.}$$

Also by interpretation of the effect of curare,

$$A - C = \text{the metabolism due to shivering.}$$

Since

$$\begin{aligned} A - B &= \text{centrally stimulated metabolism} \\ \therefore B &= \text{peripherally stimulated metabolism} \end{aligned}$$

By observation

$$\begin{aligned} A - C = B &= \text{shivering metabolism} \\ \therefore C &= \text{nonshivering metabolism} \end{aligned}$$

But by observation

$$A - B = C$$
$$\therefore C = \text{centrally stimulated metabolism}$$

If the above is true, then diathermy plus curare treatment should equal BMR or zero.

Since diathermy plus curare treatment $= D$, and D approximates BMR or zero, then the conclusion that $B + C = A$ is acceptable.

Therefore, the following conclusions may be drawn.

(1) As postulated by Bernard, Rubner, and Cannon, a nonshivering form of thermogenesis does exist and is demonstrated here quantitatively.

(2) Nonshivering thermogenesis of unacclimatized rats is stimulated primarily by central temperature changes and contributes 45 per cent of the cold-induced metabolism.

(3) In the unacclimatized rat, shivering contributes about 55 per cent of the cold-induced metabolism and this shivering is stimulated primarily by changes in skin or peripheral temperature.

(4) The postulate of Richet, which proposes that the cold-induced metabolism consists of a centrally and a peripherally stimulated fraction, appears to have been demonstrated.

The fate of these two fractions as a result of cold acclimatization in the rat provides strong evidence of the importance of nonshivering thermogenesis, and likewise demonstrates physiological changes as a result of cold adaptation.

Effect of Acclimatization on Thermogenic Factors

Figure 7 shows the fate of shivering in 3 groups of rats exposed to 3 different environmental temperatures for 30 to 50 days. The ordinate represents percentage change of shivering and percentage change of the cold-induced metabolism. Shivering activity was measured by integrating EMG recordings of muscle-action potentials. The 3 upper curves are metabolic rates; the 2 lower curves are shivering activities of the groups exposed to 13° and 6° C., respectively. Shivering activity of the 2° C.-exposed group was not obtained. Shivering activity is seen to decrease and disappear at 25 to 30 days of exposure, while oxygen consumptions were maintained at levels well above basal. These findings confirm the independent observations of Sellers *et al.*,[6] Heroux *et al.*,[7] and Cottle and Carlson,[8] and they demonstrate that in the acclimatized rat all of the metabolism is arising from nonshivering sources. With the assistance of the technique of curare and diathermy, the disappearance of shivering was confirmed and the appearance was demonstrated of a nonshivering but peripherally stimulated thermogenesis in addition to that already demonstrated in the unacclimatized rat.[5] The conclu-

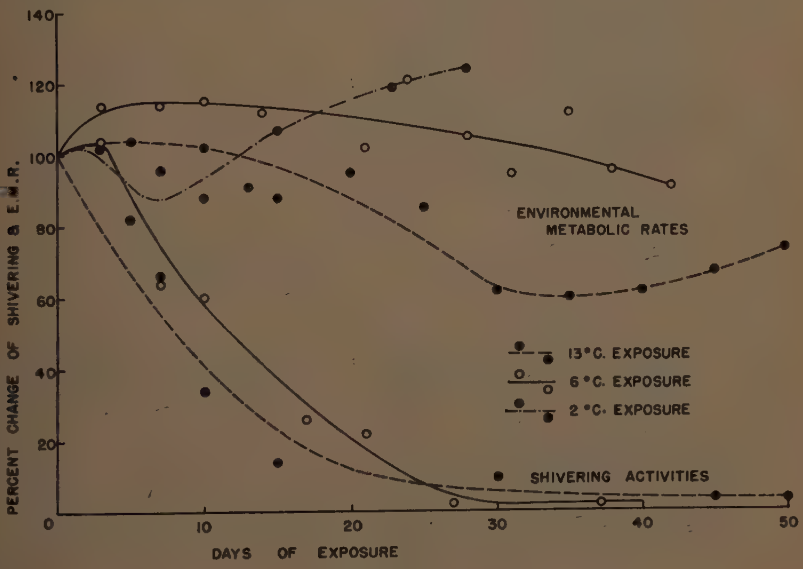

Figure 7

sions drawn from the results of these studies are presented in FIGURE 8, where various thermogenic fractions that contribute to cold-induced metabolism in the acclimatizing rat are depicted. The ordinate in each of the curves is the contribution of the various thermogenic fractions expressed in percentages of the total cold-induced metabolism. The second curve is the relative contribution of shivering, which is 50 per cent in the unacclimatized rat and 0 per cent in the fully acclimatized rat, as measured by shivering activity and oxygen consumption of curarized animals. The third curve represents the development of a nonshivering fraction stimulated by peripheral cold receptors. This fraction appears to replace the thermogenic duties previously performed by shivering. The fourth curve is the centrally stimulated nonshivering fraction present in unacclimatized rats and unchanged by acclimatization. Therefore, during the acclimatizing period, total metabolism at any time is the algebraic sum of these fractions. Furthermore, the dual control proposed by Richet also appears to hold true for cold-acclimatized rats.

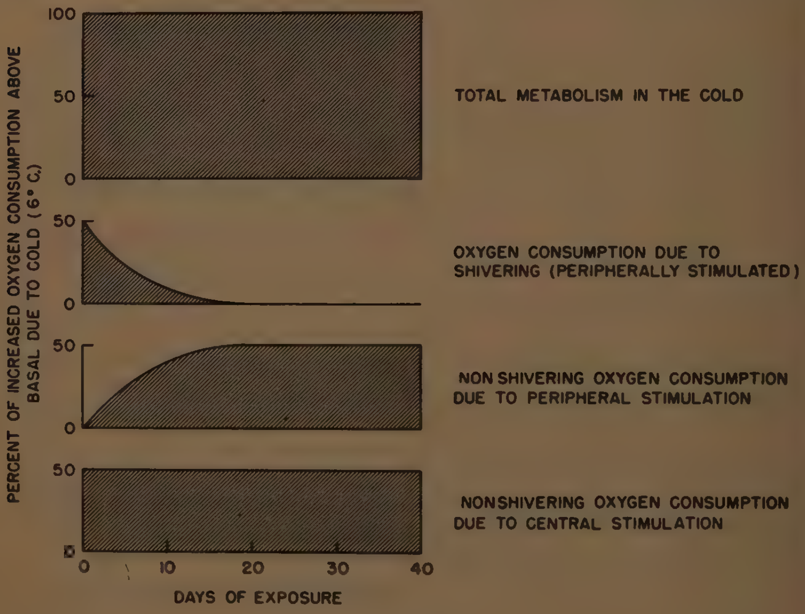

FIGURE 8

In man, similar physiological changes as a result of prolonged exposure to cold may be observed.[19, 20] These changes may be seen to occur as a result of seasonal change, as well as a result of deliberate exposure to cold. FIGURE 9 depicts the change in shivering and heat production resulting from the change of seasons from summer to winter. The 6 subjects in this experiment were deliberately exposed to a temperature of 14° C. for only 1 hour in each month for measurement purposes. The remainder of the time they lived their normal lives. There are 2 chief points of interest in this figure: first, shivering activity required a period of 3 months to reach near-zero levels of activity; second, heat production in February and in the absence of shivering was still 30 per cent above basal, indicating the presence of a nonshivering thermogenesis in man. Since the subjects received only 1 hour of deliberate cold exposure per month, these changes are presumed to have been due to seasonal change.

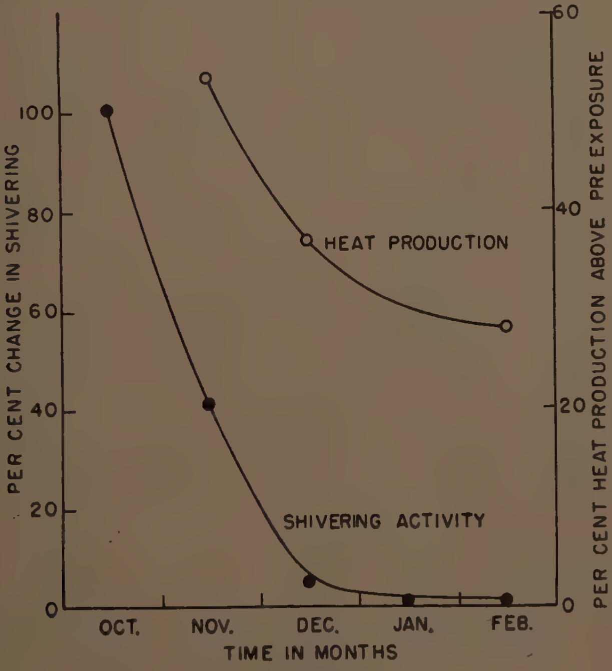

FIGURE 9

FIGURE 10 shows similar changes in 10 human subjects who were exposed for 8 hours daily for 32 days to an air temperature of 12.5° C. The fall in shivering activity in the first 10 days is dramatic, indicating that the process of acclimatization in man can be achieved deliberately without undue difficulty. The fact that the metabolism is still 33 per cent above basal again points to the presence of nonshivering sources of heat production in man. It was observed also that heat loss via the respiratory system is lessened considerably by acclimatization and accounts for a great proportion of the diminution in heat production that occurs during acclimatization.

Factual clues as to the nature of nonshivering thermogenesis are scarce. The recent work of Hsieh and Carlson[21] gives some inkling of the important chemical changes that may be taking place. They showed that the calorigenic effect of noradrenalin is increased approximately four times in acclimatized rats, as compared with those unacclimatized. These evidences of physiological change resulting from acclimatization appear to be important in that they are associated with an increase of resistance to frostbite and hypothermia.

In the rat, Blair and Dimitroff[22] have shown that acclimatization of 50 to 60 days increases the survival time of rats from a mean of 10.1 hours to a mean of 35.8 hours when exposed to −15° C. Furthermore, this period of

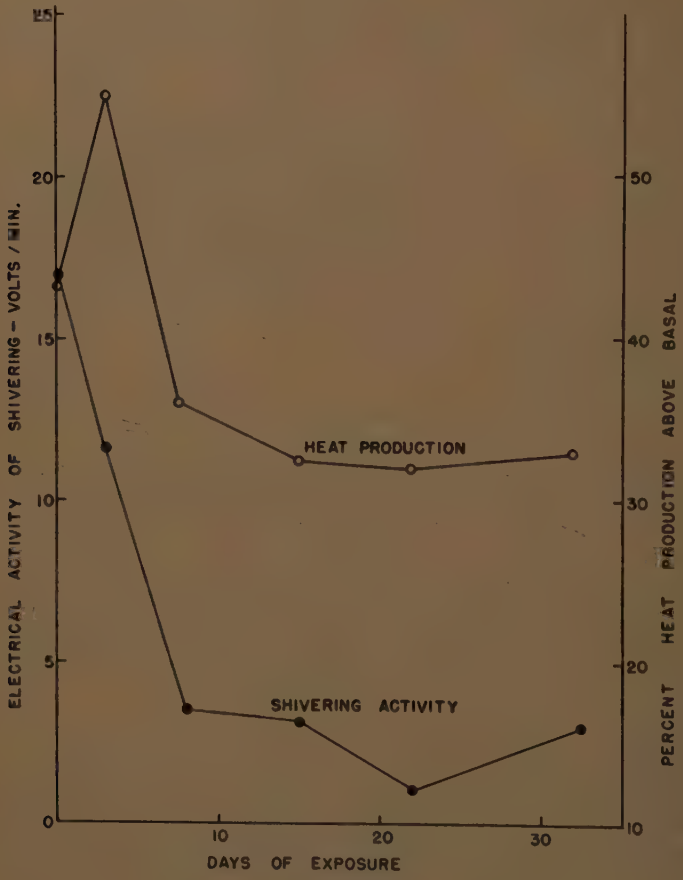

Figure 10

acclimatization greatly increases resistance to hypothermia, as depicted in Figure 11, where the colonic temperature of acclimatized rats in the upper curve indicates complete resistance to hypothermia when exposed to a temperature of −15° C. for 8 hours. On the other hand, the unacclimatized animals show a marked development of hypothermia under the same conditions.

The implications of these findings in experimental hypothermia should be obvious in that the thermal background of experimental animals could affect seriously the reproducibility of criteria and results.

In the light of insufficient information, it is usually presumed that heat and cold acclimatization are mutually antagonistic in that one destroys the other. Stein has presented evidence indicating that heat acclimatization is not affected by cold exposure.[23] My observations on the effect of heat acclimatization upon cold acclimatization indicate that the two mechanisms can, indeed, coexist and are not mutually exclusive.[24]

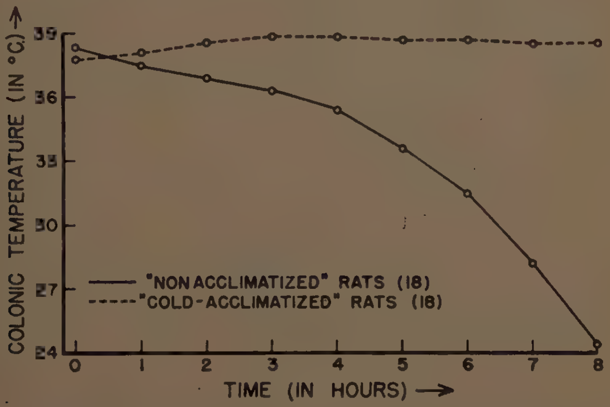

Figure 11. Mean colonic temperatures of rats during 8 hours' exposure at −15° C.

Summary

Two main sources of thermogenesis during cooling are demonstrable: a shivering source and a nonshivering source. The regulation of the thermogenic contribution of shivering does not seem to be a simple stimulus-response mechanism and, to date, the complexities defy clear analysis. The factors that give rise to nonshivering thermogenesis in both the unacclimatized and acclimatized state are relatively uninvestigated. The probable roles of humoral, neural, biochemical, and enzymatic systems are receiving attention, but only cautious postulations of the mechanisms involved are possible at this time. In the acclimatizing homeotherm, the few facts available indicate that substantial physiological changes are taking place. These changes greatly modify not only thermogenic factors, but also resistance to the pathological conditions associated with cooling. In man the changes due to acclimatization appear to be associated with a substantial decrease in energy requirements for a given cold stress.[19, 20, 25] Although this seemingly increased efficiency can give rise to much exciting conjecture, it does appear that the decreased energy requirement is due in large part to the decreased heat loss via the respiratory system. In the stabilized hypothermic state, both shivering and nonshivering thermogenic factors may be demonstrated.[10, 11, 13] Finally, the assumption that heat and cold acclimatization are mutually exclusive can no longer be upheld with any degree of certainty.

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TEMPERATURE GRADIENTS DURING HYPOTHERMIA

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It has become abundantly apparent that thermal gradients within the body can be large during rapid changes of body temperature by any method. These gradients are of importance in selecting a site for temperature measurement, in estimating the degree of overshoot or "coasting" of the temperature when cooling is stopped, in estimating the safe time of ischemia for various tissues, in studies of the physics of heat transfer, and in considering the problem of bubble formation during perfusion with cooled blood.

In this paper I shall take the heart temperature, as measured in the blood in the ascending aorta, to be the standard of core temperature. Temperature in the 2 ventricles has been shown to differ[1, 2] less than 0.08° C. and lung temperature may be assumed to equal left ventricular temperature. Organs with high perfusion, such as brain and kidney, may be assumed to follow heart temperature passively.

Bazett[3] suggested that the temperature of blood in the peripheral arteries might be altered by heat exchange directly with the adjacent veins, the arrangement constituting a heat conservation device. This countercurrent exchange mechanism has been demonstrated in many aquatic and terrestrial mammals and birds.[4] The amount of temperature change in the artery depends not only on the temperature of the returning venous blood, but also on the temperature of other adjacent tissues and upon the rate of blood flow through the artery.

There is some evidence concerning the accuracy and variability of rectal temperature and its relation to other deep body temperatures. Of course, a thermometer, if surrounded by fecal matter, may respond sluggishly to rectal temperature changes. Recently, Horvath and his co-workers[5] have reported that the highest temperatures in the normothermic dog body are in the rectum, the hepatic veins, and the coronary sinus. Bazett *et al.*[6] have shown that the rectal temperature can be influenced by the temperature of the blood in the internal iliac veins. Mead and Bommarito[7] verified this as follows: in man, the venous return from the leg was interrupted by a tourniquet, allowing cooling of the blood congested in the skin. Following removal of the tourniquet, the cold blood passed up the iliac vein, and rectal temperature fell as much as 0.3° C.

In the normothermic subject these body temperature gradients may be small but, when body temperature is rapidly altered as in immersion hypothermia, they may become very large. In the course of a study of the effects of anesthesia and hypothermia on respiratory physiology, it became apparent that rectal temperature could differ seriously from heart temperature.

In the search for a reliable and convenient index of heart temperature, the lower esophageal temperature was investigated.

The gradients between esophageal, oral, and rectal temperatures have been investigated by Cranston *et al.*,[8] who found the highest esophageal temperature just above the cardia. These investigators also noted an abrupt fall at the level of the trachea. Cooper and Kenyon[9] compared the rectal and esophageal temperatures with temperature taken on the surface of the aorta in man during hypothermia. Having seen gradients of 0.3 to 2.2° C. in a series of 10 patients cooled to 31° C., they also agree that rectal temperature may be quite misleading. They reported maximum differences between para-aortic and esophageal temperatures of 0.25° C.

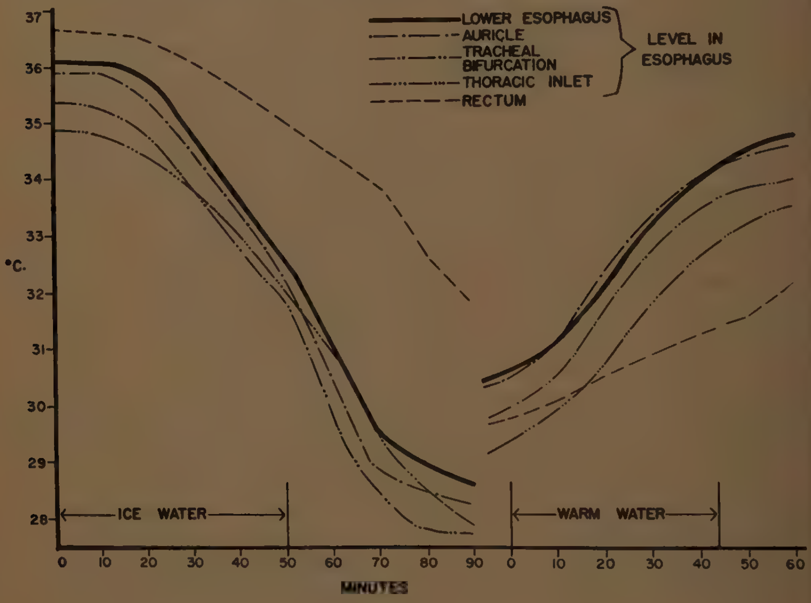

FIGURE 1

Stupfel and I[10] obtained experimental evidence that the lower esophagus, below the atrium, is a suitable site for determining heart blood temperature. In 6 dogs, thermocouples were introduced retrograde through the carotid artery to the region of the aortic valve. During rapid cooling and rewarming by immersion, this aortic temperature agreed with lower esophageal temperature to within 0.5° C. at all times. In 2 patients needle thermocouples were introduced into the left auricle before and after inflow occlusion under hypothermia. These indicated exactly the same temperature, to within 0.1° C., as the thermocouple in the lower esophagus, whereas the rectal temperature in both patients was more than 1° C. higher.

The temperature gradient along the esophagus was studied in 5 adults during surface cooling. Esophageal temperatures were recorded with 4 thermocouples in a single catheter at distances from the nostril of 27 cm. (thoracic inlet), 34 cm. (tracheal bifurcation), 39 cm. (auricle), and 47 cm. (lower esophagus). The record of one of these patients is shown in FIGURE 1. The exact location varied somewhat with body size and was checked radiographically in each case. Taking the lower esophageal temperature as correct, the temperature in other sites varied as follows (TABLE 1): the temperature near the tracheal bifurcation remained about 1° C. low during normothermia, cooling, and rewarming. The region of the auricle was about 0.5° C. low at reduced body temperatures and 0.2° C. low at normal temperatures. The thoracic inlet temperature, although usually low, behaved in a sluggish and unpredictable manner (this has been found true of nasopharyngeal temperature also).

TABLE 1

AVERAGE TEMPERATURES IN °C. IN 5 PATIENTS DURING HYPOTHERMIA AS RECORDED IN THE RECTUM AND IN 4 LEVELS IN THE ESOPHAGUS

Site	Before immersion	End of cooling	Before rewarming	End of rewarming
In esophagus				
Thoracic inlet	35.8	33.5	29.2	34.0
Tracheal bifurcation	35.3	32.3	29.1	33.8
Auricle	36.0	32.9	29.6	34.5
Lower esophagus	36.2	33.4	30.0	34.7
In rectum				
	36.6	34.2	29.8	33.5

Errors in Rectal Temperature During Hypothermia: Surface Cooling and Rewarming

Temperature measurements were made during experiments on 32 mongrel dogs (av. 11 ± 3 kg.) and during surgery on 17 patients.

In dogs during cooling and rewarming the colic temperature at 20 cm. usually fell and rewarmed more rapidly than the other recorded temperatures. Mean gradients of more than 2° C. were observed when cooling had reached 22° C. and when rewarming was complete. These gradients were highly variable in these animals, the rectum remaining warmer than the esophagus in some dogs and, in others, as much as 4° C. cooler throughout most of the cooling period. When the ice or ice water was removed cooling gradually ceased, first in the colon, then elsewhere. The large thermal gradient declined to values of about 0.3° C. after 30 to 60 min., the colon remaining cooler.

During hypothermia, the temperature in the rectum and colon varied considerably with the depth of insertion of the thermocouple. Whereas in the normothermic animal the variations of these temperatures with depth are less than 0.3° C., in a series of 5 dogs during hypothermia an area was found in each, between 10 and 20 cm. from the anus, where the temperature was 0.5° to 1.0° C. colder than in either the rectum or the deeper colon. This gradient between rectum and colon increased as cooling progressed.

As noted previously, Bazett has demonstrated that the rectum can be cooled by cold blood in the iliac veins. In order to localize the source of this differential cooling, heat or cold was applied at various discrete sites of the animals' anatomy. The temperature in this coldest zone of the colon could be lowered or raised selectively by covering the dogs' abdomen with an ice bag or an electric blanket. At autopsy, thermocouples were shown to be deep within the abdomen, suggesting that direct conduction of heat through tissues was an unlikely explanation of the observed effect. Heat or cold applied to the groins and thighs was found not to produce this effect. Heat or cold applied to the dorsolateral buttock area (away from the anus) resulted in alterations of the rectal temperature at a depth of 6 to 8 cm., with little effect on other deep body temperatures.

Esophageal and rectal temperatures have also been recorded in 17 patients during immersion hypothermia, the subsequent surgery, and the rewarming period. Patients were removed from the ice water when esophageal temperature had fallen to 33° to 33.5° C., usually after 1 hour, at which time rectal temperature ranged from 31° to 36° C. The temperatures continued to fall, reaching an average of 29° ± 1° C. (esophageal) at about 150 min. after the initial immersion. In 15 cases the rectum cooled more slowly than the esophagus, the largest gradient being obtained shortly after removal from the bath. In these 15 the maximum observed gradient averaged 1.9° ± 0.7° C. In 2 cases the rectum cooled more rapidly than the esophagus, maximum gradients of 1.2° and 1.9° C. being observed. No patient has been observed in whom rectal and lower esophageal temperatures agreed to within 0.7° C. at all times.

Blood Cooling and Rewarming

It was thought that cooling of blood in an external shunt from femoral artery to vein might selectively lower the rectal temperature as the cold blood flowing up the iliac vein came into proximity with the rectum. Four cooling experiments performed in two dogs showed that this does not occur. The heart temperature fell most rapidly, and no direct effect on rectal or colic temperature from the cold iliac venous blood was noted (TABLE 1).

Effects of Vagotomy on Internal Temperature Gradients

While investigating thermal gradients during surface refrigeration in dogs, I incidentally noted that after a bilateral section of the cervical vagosympathetic nerve, the colic temperature fell very much more rapidly than the cardiac and esophageal temperatures. The experiment was repeated in 8 vagotomized dogs. For an average esophageal temperature of 23° C., the colic temperature at 20 cm. averaged only 16.2° C., so that a thermal gradient of 6.8° C. existed between them, this gradient varying between 2° and 11° C. It was found that the gradient occurred within 3 min. after the dogs were covered with ice. In the intact animals, for the same esophageal temperature, the gradient was only 1.6° C. and developed gradually over the course of an hour. I have not been able to reproduce this phenomenon by intravenous injection of atropine (0.5 to 6.0 mg.).

When 3 or 4 thermocouples were placed at different depths in the colon, it was found again, in these bivagotomized dogs, that the coldest point was between 10 and 22 cm. The average temperature gradient between coolest and warmest parts of the colon was 4° to 6° C. and, in one case, 12° C. Furthermore, this portion of the colon is rewarmed more quickly than the other internal regions when the dog is immersed in hot water, and is selectively cooled or rewarmed when the skin of the abdomen is covered with ice bags or an electric blanket.

Vagotomy failed to alter the thermal gradients produced by arterial blood cooling or rewarming. In six normothermic curarized dogs exposed to the ambient room temperature bilateral vagotomy did not significantly affect the temperatures in the thoracic aorta, superior vena cava, esophagus, colon, and rectum. It did warm the ear, since the sympathetic fibers accompanying the vagi were also cut.

Discussion

Deliberate induction of thermal gradients, or differential hypothermia. Many investigators have attempted to cool the brain, liver, or heart differentially. In the case of the brain, this is done by passing cold blood into carotid arteries. Gollan *et al.*[11] have rapidly cooled the heart and highly perfused organs by cooling the blood in a pump oxygenator. They present a formidable rationale for this method of combining hypothermia with extracorporeal circulation for prolonged cardiac surgical procedures. They have cooled dogs to nearly 0° C., with survival, and find that rectal temperature fails to follow heart temperature, with differences of 20° C. Their published curves show a differential between esophageal and right heart temperature as great as 4° C., but the esophageal level was not stated, and the cold blood was being introduced into the aorta, not reaching the right heart until it perfused through peripheral capillary beds, after which it was drained out the femoral catheter, and not into the right heart.

The liver has been differentially cooled by flooding the peritoneal cavity with cold saline. Huggins *et al.*[12] obtained gradients of 10° C. in dogs, and report on one patient.

The effect of changing temperature on gas solubility must be remembered by users of blood-cooling techniques. To prevent bubble formation, the cooling should be done after oxygenation, and the warming process must be done before oxygenation. A coil without an oxygenator probably should never be used for rewarming because of the danger of bubble formation.

When hypothermia was induced rapidly, thermal gradients always appeared. In 1946 Libelli and Poggi[13] noted thermal gradients between brain and rectum of guinea pigs cooled by immersion. Haterius and Maison[14] observed gradients of as much as 3° C. between liver and rectum in dogs cooled by immersion to 15° C. (rectal). Hegnauer and Penrod[15] noted that dog brain temperature during rapid cooling might be several degrees higher than rectal temperature, with heart temperature being intermediate. Rectal and gastric temperatures were compared in volunteers immersed in cool water (20° to 25° C.) by Spealman.[16] The rectal temperature, slightly higher before immersion, averaged 0.8° C. lower during immersion.

My results indicate that the relationship between rectal and other deep body temperatures is not predictable, and that large gradients sometimes develop during rapid cooling. These gradients may be in either direction. Generally, the rectum cools faster in dogs and slower in patients than the heart.

A further difficulty associated with rectal temperature proved to be the variation in temperature with depth or position of the sensing element. Although this was most profoundly true of dogs after vagotomy, where variations of 12° C. with position were noted, it was frequently observed in both thin and heavy adults, where differences of 1° C. were noted between thermocouples no more than 4 cm. apart at depths of 15 cm. or more. Often the deeper thermocouple was cooler during cooling, excluding effects of cold water leaking through the anus.

The method of cooling appears to influence the thermal gradients. Thus, in the dog, surface cooling usually resulted in the rectum cooling more rapidly than the heart, whereas with blood stream cooling, femoral artery to vein, the fall in rectal temperature lagged behind the heart.

With regard to esophageal temperatures, it is interesting that both dogs and men showed a consistent pattern, the coolest area of the esophagus being near the lower trachea. Since endotracheal tubes were present, it is believed that the cooling is due chiefly to evaporation in the lower trachea. The temperature adjacent to the auricle was usually slightly cooler than in the lower esophagus. This may result from the proximity of liver and aorta to the lowermost esophagus. The thoracic inlet temperature followed lower esophageal temperature closely during cooling, but usually lagged somewhat behind during rewarming. The esophagus below the auricle was uniformly very close to the temperature of the heart as measured in the outflowing blood.

In much of the now extensive literature concerning hypothermia only the rectal temperature has been measured. In view of the considerable uncertainty regarding rectal temperature during rapid changes in body temperature it seems reasonable to seek another more reliable site. The lower portion of the esophagus from the auriculoventricular boundary to the cardia seems well suited for this purpose. It is readily accessible during anesthesia by means of thermocouple or thermistor elements mounted on suitable rubber or plastic catheters.

It is not clear why vagotomy should have such a consistent and profound effect on the rate of cooling of a certain area of the colon. The phenomenon of local cooling has not been reported previously. The distribution and function of the vagi in the large intestine is somewhat unsettled, although histological and physiological evidence supports the presence of vagal fibers in the descending colon.[17, 18] I recorded total portal blood flow in one dog and found no change after vagotomy. It may be that vagotomy changes the pathways by which venous blood from the abdominal skin returns to the vena cava, allowing it to flow in close proximity to this area of the colon.

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METHODS FOR INDUCING HYPOTHERMIA AND REWARMING

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The actual method of inducing hypothermia is not as important as the management of the cooling process. In discussing methods, there are two essentially different techniques of inducing hypothermia in patients.

The technique of extracorporeal cooling of the blood was first demonstrated by Boerema *et al.*[1] and Delorme[2] and used extensively in London, England by Brock and Ross.[3] Arteriovenous and venovenous cooling have been recommended. Brock and Ross used the venovenous cooling with a pump and refrigerating device in a large number of cases. They claimed that this technique of cooling would allow opening of the chest and examination of the heart at normal body temperature, whereupon extracorporeal cooling could be instituted if a hypothermic operation was decided upon. This minimized the length of time that the patient was hypothermic. These investigators suggested a further advantage in cases where one encountered an unexpected lesion requiring the open-heart technique and the cooling process could be carried out in a short time. This also allowed rapid rewarming.

One of the chief disadvantages of this technique is the necessity for cannulating the veins and the attendant problems of extracorporeal circulation. In the last two or three years there have been two developments that make this method of hypothermia less attractive. In the first place, diagnostic techniques have improved considerably with better angiocardiography, left-heart catheterization, dye-dilution curves, and intracardiac phonography. We are less often in doubt as to the diagnosis preoperatively. The second development, which effects this technique, is the remarkable improvement of cardiac bypass machines. It is the feeling in Toronto, where both hypothermia and bypass are used, that hypothermia should be used for the simpler lesions when there is no doubt of the diagnosis and associated anomalies have been ruled out reasonably. Otherwise, the patients are operated upon with the heart-lung pump.

Hypothermia has been incorporated in experimental[4] and, more recently, in clinical[5] heart-lung procedures. This allows lower flow rates and it may also be used to cool patients to temperatures below the usual 28° C. with more safety than that which would be afforded by simple extracorporeal cooling without oxygenator. This use of hypothermia has a bright, immediate future.

There are several means of surface cooling that constitute the alternative method of inducing hypothermia. These are: immersion in water, cooling blankets, packing in ice or ice bags, and irrigation of the pleural cavity with cold saline.

Immersion in cold water, or ice water, is not an attractive method of cooling adults, although it may be a few minutes faster than the combination of blankets and ice bags. In children and infants it is an acceptable method of cooling, although W. T. Mustard of the Hospital for Sick Children, Toronto, has found that simple ice bags are an efficient and rapid method in treating small children. In operations upon larger children and adults, the Therm-O-Rite cooling blankets are used, but these are not efficient unless the room is air-conditioned and, in addition, about eight ice bags must be used on the patient under the blanket. These are placed over the groin, abdomen, axilla, and in the clavicular regions. This technique is simple, and the actual cooling period for an average adult, with both blankets and ice, is about 50 min. (FIGURE 1).

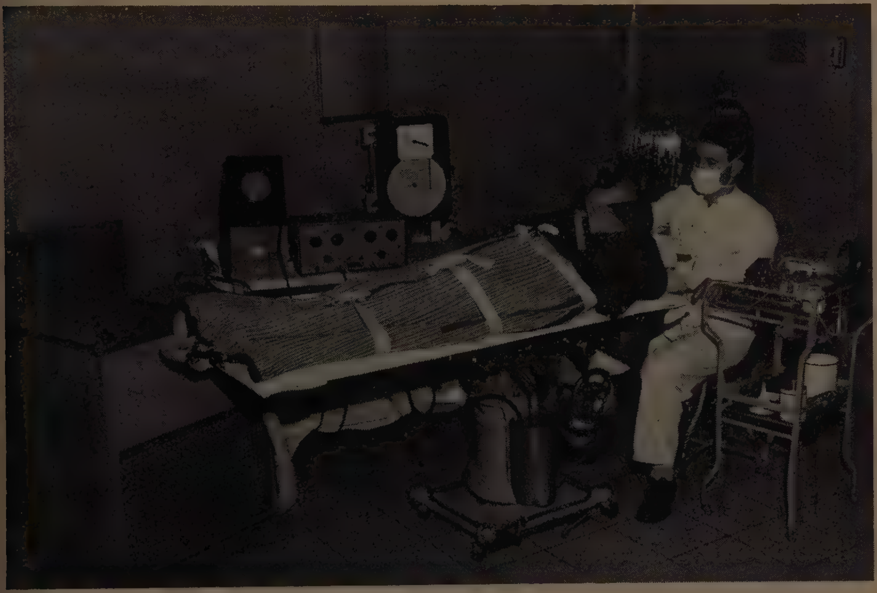

FIGURE 1. Cooling blankets for hypothermia. This is an effective and rapid method of cooling adults, provided that there is control of the operating room temperature and that six or eight ice bags are applied directly on the patient under the blankets.

The Neurosurgical Service at the Toronto General Hospital under E. H. Botterell has used hypothermia extensively. The service initially used ice water, but now uses only ice in the bath, and the bath is primarily used for rewarming, FIGURE 2. The irrigation of the pleural cavity with cold saline does not appeal as a routine method of inducing hypothermia, but it is worth remembering in case one wishes to lower the body temperature after the chest has been opened and no special facilities are available.

Control of the Cooling Process

In a brief presentation the control of the cooling process may thus be discussed under management of the four essential problems that arise in clinical hypothermia. These are: (1) methods of controlling the drift of body temperature; (2) the reduction of cardiac irritability; (3) the control of rewarming shock; and (4) the occasional bleeding tendency that occurs in hypothermia.

(1) *Control of body temperature drift in hypothermia.* The problem of drift of body temperature after active cooling is a significant one in very young children and infants, or where a very rapid technique of cooling is used. One of the best controls of the body temperature is experience with the particular method that one uses. The more rapidly the patient cools, the further will be the drift, once active cooling is stopped. One must be aware of the very labile thermoregulating mechanism of the infant who may be cooled to 28° C. with a 6-min. exposure in a cold bath. If a very heavy individual is cooling rapidly, considerable drift from the large body mass must be expected.

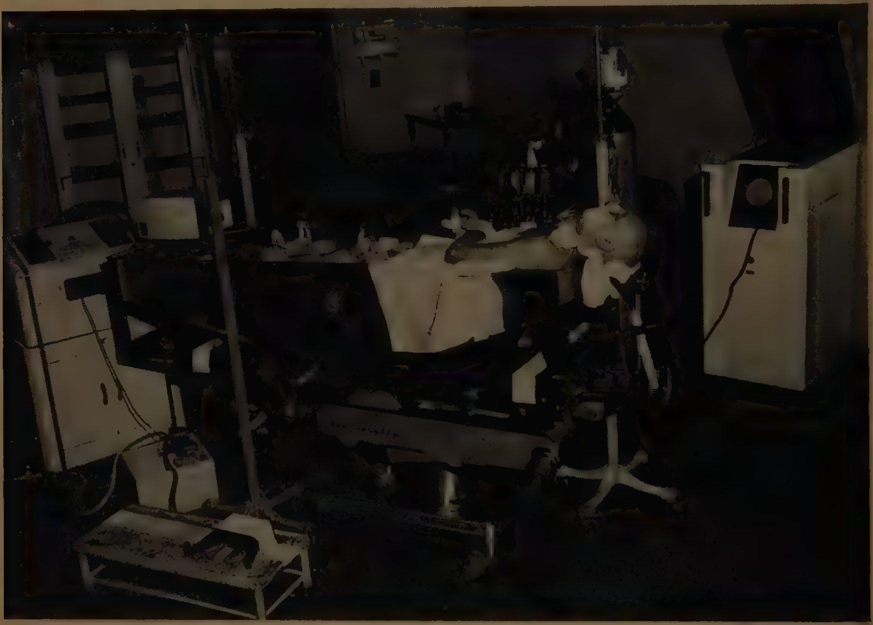

FIGURE 2. Cooling by means of ice chips for neurosurgery under hypothermia. The patient remains in the special bath during operation, and rewarming can be instituted at a moment's notice by the addition of thermostatically controlled warm water.

At the Toronto General Hospital, in addition to making use of considerable clinical experience, we have had the added guide of comparing rectal and esophageal temperatures. FIGURE 3 illustrates the relationship between these two readings during an open-heart hypothermia operation. The esophageal thermocouple should lie opposite the heart. Its position is regulated after cooling has started, and there is a point in the midesophagus where the temperature is one or two degrees below the temperature in the upper or lower esophagus. Here the thermocouple lies against the heart and reflects the temperature of the blood returning from the periphery. During cooling the esophageal temperature is 1° to 4° C. below the rectal temperature.

An indication that the drift in body temperature after active cooling is near an end is the reduction in the temperature difference that occurs between the esophageal and rectal readings. Once these two readings become equal, it can be assumed that the drift has ceased.

In a patient who is cooling rapidly, there is usually a greater temperature difference and this, in turn, will reflect a greater drift (esophageal-rectal, point A in FIGURE 3). After the temperature is stabilized, the esophageal temperature becomes higher than the rectal temperature and remains so during rewarming. The sudden influx of cold blood by intravenous transfusion may be indicated in the esophageal temperature recording. Although the patient is prepared and draped during the drift period, I like to start actual surgery only when there is evidence that the drift is near an end.

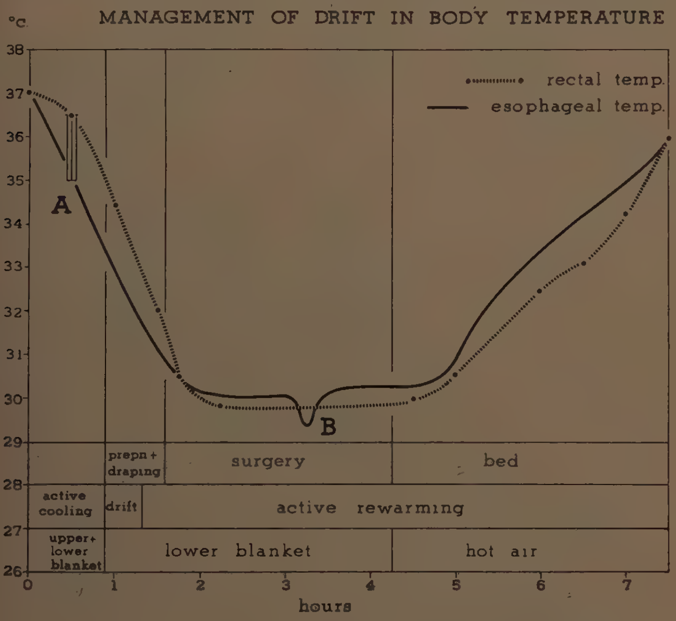

FIGURE 3. This graph illustrates one method of controlling the drift in body temperature by means of blanket and ice bag cooling. Once active cooling has stopped, the esophageal and rectal temperatures approximate; once they are equal, the further fall is seldom more than one-half degree C. in body temperature. It is preferable to withhold surgery until the two temperature lines commence to converge, point A. The greater the temperature drift, the more rapid the cooling and the greater the expected drift. The rapid infusion of blood at room temperature, at time of cardiotomy, may produce a temporary drop, as indicated.

The cooling unit is now available with a separate reservoir that will allow sudden switchover to rewarming and there is not the delay in warming the alcohol to the desired temperature. The neurosurgeons use muscle temperatures as well as rectal and esophageal temperatures as a further control of body temperature.

It may be said that, with experience and some method of control such as those mentioned, the problem of unexpected drift in body temperature does not exist.

(2) *Cardiac irritability.* Cardiac irritability and ventricular fibrillation were problems in the early days of hypothermia when the safe cooling range was not recognized clearly.

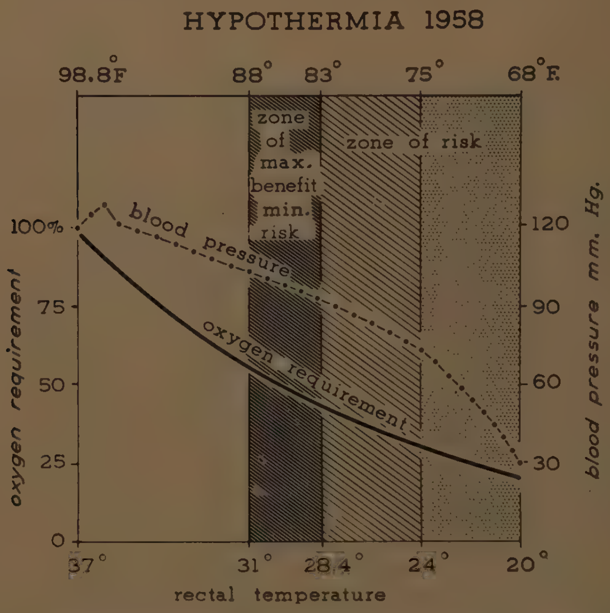

FIGURE 4. A graphic illustration of the body temperature range most suitable for open-heart surgery with hypothermia cardioplegia. In the temperature range of 28° to 31° C. the circulation may be interrupted for periods of up to 10 min. provided the cardiac function is arrested, or depressed, by intracoronary acetylcholine or Prostigmin.

In Toronto there are three surgical teams, in two hospitals, using hypothermia. More than 500 patients have been cooled to body temperatures below 31° C. There were three instances of ventricular fibrillation during cooling in the initial cases, following which a lower limit of 28° C. body temperature was adopted. Since that time there have been no cases of ventricular fibrillation prior to actual surgical manipulation of the heart. The desired temperature range is represented graphically in FIGURE 4.

As the temperature falls below 30° C., however, there is an increased cardiac irritability that is evident during cardiac surgical procedures. This was originally attributed to the blood *p*H, but the study by Waddell *et al.*[6] in our laboratory demonstrated no correlation between the *p*H and ventricular irritability, but a surprising relationship between the blood citrate level and incidence of irreversible ventricular fibrillation during surgery. This is illustrated in TABLES 1 and 2. From these tables it may be seen that the use of citrated blood produced not only a higher incidence of ventricular fibrillation

TABLE 1
EFFECT OF BLOOD CITRATE LEVEL ON VENTRICULAR IRRITABILITY

	Blood citrate (mg. %)	
	Under 20	Over 20
Number of cases	18	6
Ventricular fibrillation	3	5
Reversible	3	2

but a higher incidence of irreversible ventricular fibrillation. Calcium was used in these cases. When this is compared with operations carried out with heparinized blood the expected low citrate levels is noted; irreversible ventricular fibrillation has not been a problem. I now use fresh, heparinized blood and, at proper temperature levels, the heart does not show undue irritability. Protamine sulphate is given in amounts equal to the heparin administered after the infusion of each bottle.

(3) *Rewarming shock.* The appearance of shock and actual death during rewarming in early experimental studies has been recognized. It was my

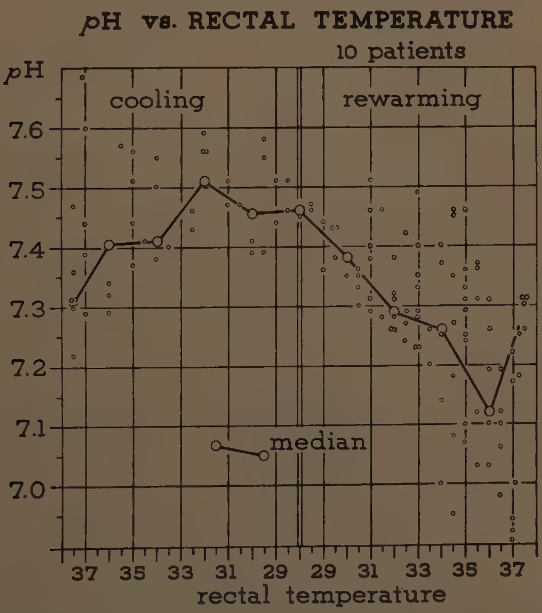

FIGURE 5. *p*H values with the early anesthetic technique. In this series the incidence of moderate or severe acidosis (*p*H values below 7.20) during rewarming was 5, or 50 per cent. Four cases of severe acidosis were associated with a condition of rewarming shock termed the acute acidotic syndrome. Alkalosis during cooling was induced purposely by moderate hyperventilation.

Table 2
Advantages of Heparinized Blood

Citrate levels	Serum citrate levels (mg. %)			
	Cases	0–9	9–20	Over 20
Citrated blood	15	4	5	6
Heparinized blood	9	9	0	0

experience, and that of investigators in many other centers, that this shocklike state developed sometimes during the rewarming period. In Waddell's study it was found that this shocklike state was related to a metabolic acidosis that could not always be corrected by hyperventilation respiratory alkalosis.

This syndrome of acute acidosis, or rewarming shock, was characterized by a progressive decline in blood *p*H to levels below 7.15 and ultimately, by an abrupt loss of consciousness, associated with respiratory inadequacy similar to that produced by curarization. A fall in blood pressure and tachycardia

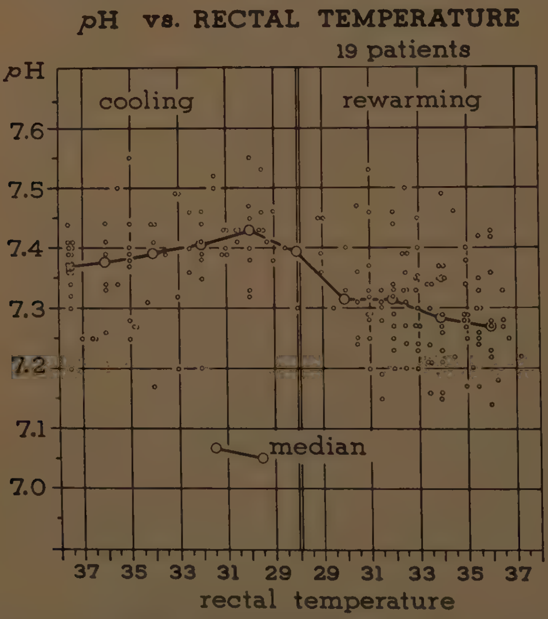

Figure 6. The current anesthetic technique using *p*H values. In order to eliminate the rewarming acidosis encountered in early cases the anesthetic technique has been altered. As a result, in this series, no patients developed clinical signs of acidosis, although 4 cases of the 19 had *p*H values in the acidosis range (below 7.20). Alkalosis during cooling was avoided purposely, and an attempt was made to maintain a normal range of *p*H throughout.

were features in some cases. With correction of acidosis by sodium bicarbonate the clinical recovery was usually dramatic. FIGURE 5 shows the tendency to acidosis in the rewarming period in 10 patients, 5 of whom developed some degree of rewarming shock.

It has been found possible to counteract this metabolic acidosis by a method of anesthesia. Since it is a metabolic acidosis, it is supposed that there is an accumulation of metabolites in the tissue due to the intense

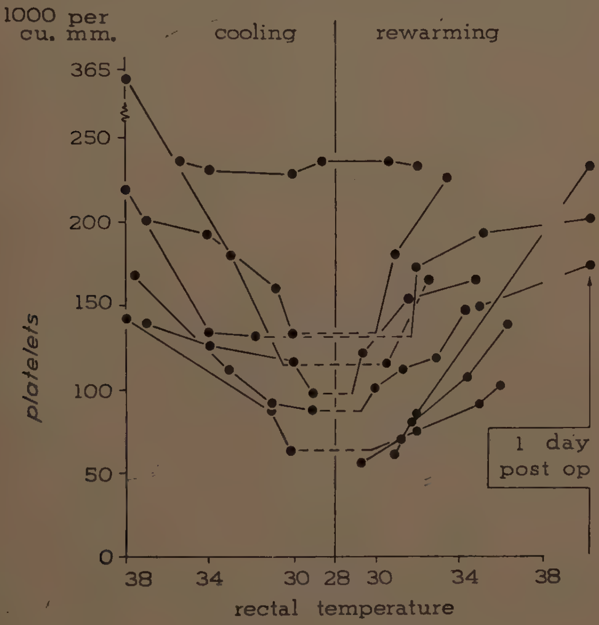

FIGURE 7. Platelet counts in hypothermia. A significant thrombocytopenia (average drop of 43 per cent) was observed in 8 of 9 patients. In each case the platelets returned to normal upon rewarming. One of these patients, with the lowest platelet count, showed an abnormal bleeding tendency. Study of coagulation factors and cations has not explained this as yet.

peripheral vasoconstriction with ordinary anesthesia and those liberated during the rewarming period. It has been found that either the use of the lytic cocktail drugs (largactil and Phenergan) or the use of a small amount of ether throughout the period of cooling prevents this rewarming acidosis, probably by maintaining the peripheral circulation. FIGURE 6 illustrates the *p*H values in 19 patients in which there were no cases that developed the rewarming shock syndrome. This effect was obtained by the lytic cocktail or ether. It may be noted that no attempt at hyperventilation or respiratory alkalosis is made during the cooling period in order to preserve available base. Shivering is also a factor that should be controlled in the rewarming period. This is easily controlled with largactil.

(4) *Occasional bleeding tendency in hypothermia.* Most surgeons with experience in hypothermic surgery occasionally have encountered a patient

with a very abnormal tendency to bleed. This is a general oozing of all the cut surfaces and the only consistent abnormality of the blood that might explain this has been the development of thrombocytopenia during cooling. This has been observed in animals but Waddell *et al.*[6] and Wensel and Bigelow[7] have demonstrated the effect in humans. FIGURE 7 demonstrates a significant thrombocytopenia, with average fall of 43 per cent, in 8 of 9 patients. As previously observed, the platelets return to normal on rewarming. One of these patients with the lowest platelet count showed an abnormal bleeding tendency. Studies of coagulation factors and cations could not explain this tendency to bleed. The use of heparin was studied in our laboratory by Wensel and reported by Ellis *et al.*[8] It has been fairly well established that the platelets are sequestrated principally in the portal system and appear on rewarming. During microscopic *in vivo* studies of the circulation, R. O. Heimbecker and I observed clumps that appeared to be agglutinated platelets

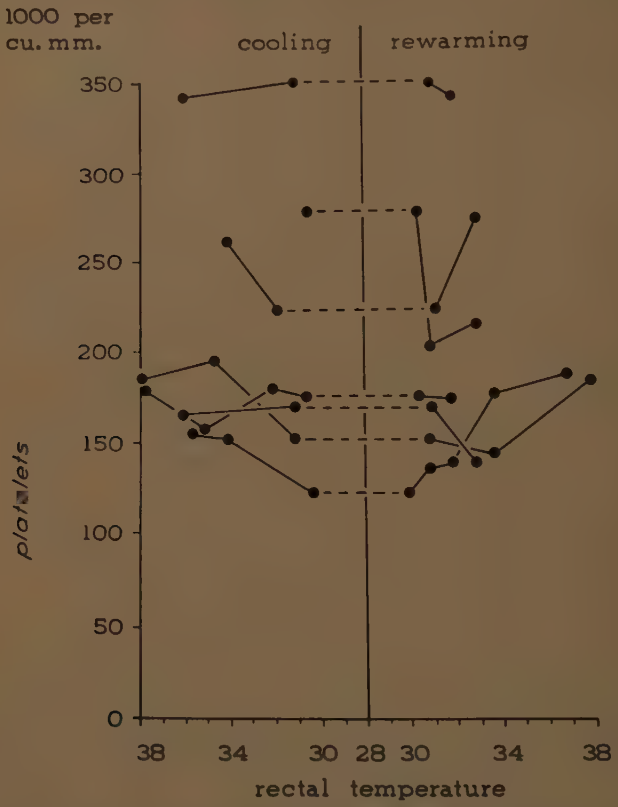

FIGURE 8. Platelet counts in hypothermia, illustrating action of heparin. This graph shows the effect of heparin administered prior to cooling in 7 open-heart operations. The average platelet drop was over 19 per cent, compared to 43 per cent without heparin. No abnormal bleeding was observed in any cases.

in the hypothermic animal. Accordingly, heparin has been used in a series of patients prior to cooling. Intravenous heparin, 15 to 20 mg., is given before cooling is started; the effect on the platelets is indicated in FIGURE 8. In this series of patients the average drop in platelet count was 19 per cent compared to 43 per cent without heparin, a significant difference, and there was no bleeding tendency. Since that time, we have used heparin routinely before cooling without encountering significant bleeding tendency in 20 cases of open heart surgery.

It is interesting that this does not seem to be as great a problem in the hypothermia surgery of children. This may be explained by some essential difference in their platelets.

Rewarming

The range of hypothermia currently in use for open heart surgery is 28° to 31° C. body temperature. In this range it is usually not necessary to use specific methods of rewarming, although I routinely reverse the blankets to rewarm during the operation so that rewarming has been initiated by the time the operation is completed. The patient is then placed in bed with a heat cradle and hot air, as well as warm water bottles. This allows the return of body temperature in about 3 hours in an adult, and in children at a much faster rate. During this rewarming period, one establishes an airway with *p*H estimations in worrisome cases, and the control of shivering with largactil. The Bennet respirator has been found very useful in difficult problems. The diathermy rewarming device, developed in our laboratories with the help of the National Research Council of Canada, is on hand in case more rapid rewarming is required. This device is seldom used.

The neurosurgical team has the advantage of operating only upon the head so that the patient can remain in the bath during the procedure; when the operation is completed, warm water rapidly returns the body temperature to normal.

Risk

The following clinical results may illustrate the safety of adequately managed open heart operations under hypothermia. To date the author has operated upon 35 patients with septum secundum atrial septal defects and 15 cases of pulmonary stenosis, by this method. These were over 12 years of age. There were 4 deaths, all atrial septal defects and all occurring in the elderly group with advanced pulmonary hypertension or terminal chronic heart failure. There have thus been no deaths in 40 consecutive, uncomplicated cases. The last problem to come under control has been the worry that an occasional patient will show an unusual tendency to bleed. Now, with reasonable control of the four main problems, the indications of hypothermia and open cardiotomy, with interruption of the circulation, is a safe procedure. The risk comes in the selection of cases.

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MODIFYING EFFECTS OF ANESTHESIA ON HYPOTHERMIA

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The fact that anesthesia diminishes activity of the anesthetized subject is generally accepted. The concept is also widely held that hypothermia lowers metabolism and that, consequently, it lowers activity as well. Is it not logical to assume, then, that anesthesia would enhance the effect of hypothermia?

Examination of some of the evidence at hand may indicate that such enhancement is not universally applicable. On the other hand, interpretation of what constitutes anesthesia may modify one's conclusions.

What Is Anesthesia?

A recent suggestion by Woodbridge[1] provides a basis for considering what the activities of anesthetic drugs may be expected to accomplish, and to give better understanding of the term anesthesia, but the understanding may come at the cost of increasing the complexity of the concept of anesthesia. Woodbridge suggests that there are four components of what is generally termed anesthesia. They are: (1) loss of consciousness, (2) loss of motor activity, (3) loss of reflex response, and (4) loss of sensory response. All four concepts can be measured only in mammals. Obviously, there is no consciousness measurable from single nerve activity. Perhaps any one of these factors may be measurable in lower systems. Application of cold or procaine may produce a nerve block. This can affect sensory, reflex, and motor activity, but can give no information concerning mental activity.

Data that bear on the concomitant use of narcotics and hypothermia have not all been obtained using identical concepts of what constitutes anesthesia. In the study of hypothermia, ether, pentobarbital, thiopentone, cyclopropane, morphine, ethanol, procaine, and chlorpromazine all have been called anesthetic agents. Of these, ether and cyclopropane are the only complete anesthetic agents, that is, they obtund all four factors involved. The other agents present considerable latitude of activity, and these differences probably cause variable impacts on the hypothermic state.

Tasaki and Spyropoulos[2] found that the application of a narcotic (ethanol) reduced the height of the giant axon potential of the squid, raised the threshold membrane depolarization, and decreased the conductance at the peak of activity. These effects of narcosis could be counteracted by cooling. These data seem to be opposed directly to the idea of enhancement of hypothermia by anesthesia. In the light of Woodbridge's hypothesis, however, it will be seen that the ethanol probably affected the total activity of the axon very little. Cooling seemingly caused reflex activity in response to stimulation despite the narcotic. It would appear that only partial anesthesia had been obtained. What, then, did ethanol do? Its activity toward sensory and reflex components of the human being can be measured but, with the giant squid axon, ethanol was not a complete anesthetic in the concentration used.

Cornman[3] has measured the effect of urethane and some of its derivatives (all were carbamates) on the time of division of sea urchin eggs. He observed that delay of cleavage occurred in a linear fashion when increasing concentrations of urethan were employed, and also that linear delay was observed in some species as temperature fell below 22° C. When the temperature rose above 22° C., however, a reversal occurred so that increasing temperature also delayed cleavage despite the presence of urethan. Cornman suggests that since urethane can be removed easily from the cell, carbamates do not combine strongly with the protoplasmic units involved, but are held loosely by adsorption or solution. If the binding is of this type, then, as the temperature is increased, the narcotic will be retained less easily in the cell, a fact that accounts for the direct relationship between concentration and temperature below 22° C. Above this temperature, however, heat itself may produce untoward effects. One expects most proteins to be denatured by heat at a temperature level near 50° C. The enzymes of the egg of the sea urchin exist at relatively low temperatures. Both aspects of the problem may relate to a single mechanism if we assume that carbamate inactivates an enzyme and that, above a critical temperature varying with the species, heat contributes to this enzyme inactivation. Cornman suggests that this idea may provide some transition between the "quantitation of enzyme systems and the bewildering biology of the intact organism."

Interesting as this theory is, application of hypothermia usually involves temperatures below those that promote denaturation of proteins. We ordinarily consider processes that are thought to be reversible by return to ambient temperatures.

Attempts to cool conscious animals have met with considerable difficulty. Unanesthetized rats exposed to low temperatures cool very slowly, whereas rats asleep with pentobarbital cool 10° C. within an hour. In our own experiments we observed that dogs put in a cold room (−10° C.) for 8 hours ran out merrily normothermic when the door was opened. When the same animals asleep with pentobarbital were cooled, they reached 25° C. in about 45 min.

Recently Wylie[4] has reported some experimental results bearing on attempts to find the relationship between potentiation of barbiturate anesthesia and hypothermia. He observed that a phenothiazine drug could cause hypothermia. It also could potentiate the action of hexobarbital for induction of sleep of mice within two minutes, before there was any fall in body temperature. Wylie concluded that the production of hypothermia and barbiturate sedations are separate pharmacological properties, and are primarily independent of each other.

Mental and Sensory Loss

About 1940, Dill and Forbes[5] and also Smith and Fay[6] found that, when patients were cooled to about 31° C., shivering ceased and the patients appeared to be comfortable; however, they were not relaxed. Their joints were stiff and could be moved only with difficulty by attendants. Simpson[7] states that in hypothermia the psychic and pupillary changes resemble those of pharmacological anesthesia. He surmised that the cerebrum would cease to function when its metabolism was lowered by cold. An unusual feature, he stated, is that, compared to chemical anesthesia, hypothermia gave retention of muscle tone and stretch reflexes. These two groups of workers used no relaxing agents. It seems from their observations, then, that hypothermia had produced sensory loss (freedom from pain of malignancies in Fay's patients) and some loss of consciousness. However, motor and reflex activities were still present.

Spurr *et al.*[8] measured oxygen uptake of nude men exposed to low temperatures, while a constant rectal temperature was maintained for some hours. Their oxygen consumption was 300 to 400 per cent above the control values. Bigelow[9] found that cooling the conscious animal stimulates shivering and increases the oxygen demand. Dill and Forbes[5] found that cooled patients only lightly sedated used more oxygen because of shivering and voluntary motion. Stone[10] measured oxygen consumption of men deliberately anesthetized lightly so they would shiver, and found that at 28° C. they used twice the oxygen they did at 37° C. So-called light anesthesia, then, did not block reflex and motor activity, and cold actually acted as a stimulus of these moieties.

Reflex Stimulation

Sarajas *et al.*[11] stated that proper hypothermia requires suppression of the thermoregulatory defense by anesthetics before cooling. They used pentobarbital with either ether or *d*-tubocurarine to control shivering. By examination of the adrenal cortices of the animals they attempted to show that hypothermia caused a stress, but they failed to take into account the effect of the anesthetic as a stressing agent on the adrenals. Sarajas and his associates realized that a relaxant was required to offset motor activity. Moyer *et al.*[12] found less shivering in chlorpromazine-treated animals. They stated that deep anesthesia enhances induction of hypothermia, and that the effect of chlorpromazine probably was due to its enhancement of barbiturate anesthesia.

Purpura *et al.*[13] state that it is a well-accepted fact that stimulation of the brain stem and diencephalon may induce cardiac arrhythmias, and they point out that the brain-stem reticular formation is an integration system that controls cardiac rhythm. In Purpura's experiments brain-stem stimulation, which was minimal under standard conditions, became maximal for production of arrhythmias after application of ice. These arrhythmias could be blocked by application of succinylcholine, Dibenamine, barbiturates, atropine, chlorpromazine, or procaine. The suggestion was made, therefore, that hypothermia increases the excitability of cardiac reflex mechanisms and that descending reticular effects of an inhibitory nature are susceptible to cold blockade. It is obvious that action of barbiturates in these instances was antagonistic to the reflex activity engendered by hypothermia.

Motor Activity

The last few authors mentioned realized that relaxation as well as the loss of sensation on the part of the subject were necessary for adequate hypothermia. Loss of consciousness may aid in inhibiting struggle against cooling, but that alone is surely inadequate. Loss of motor activity seems mandatory if oxygen consumption is to be minimal, and this, of course, is necessary for optimum rate of cooling. Loss of motor activity perhaps may be obtained in either of two ways: first by muscle relaxants, such as curare or succinylcholine; second, by deep anesthesia that is profound enough to prevent afferent impulses (which might be sensations if the patient were awake) from causing reflex motor activity. Cyclopropane or ether may do this. Adequate doses of pentobarbital or thiopentone *may* accomplish this end for short periods, but objective pain measurements (using the D'Amour-Smith method[14]) have indicated that barbiturates are poor analgesic agents.

One feature of clinical hypothermia, the one that at present is its most potent limiting factor, is the appearance of ventricular fibrillation at temperatures usually below 28° C. in human subjects. Various experiments have been carried out in attempts to find the cause. Some workers have wondered whether individual anesthetic agents per se might be responsible. Riley *et al.*[15] compared the effects of thiopentone and pentobarbital with and without succinylcholine. The relaxant aided in the prevention of ventricular fibrillation, but the differences between the two barbiturates studied were slight. The effect of succinylcholine was probably due to its prevention of shivering. Millar[16] states that while *d*-tubocurarine prevents shivering, it does little to inhibit autonomic reflex responses such as epinephrine secretion, so that metabolism may rise without shivering. There appears to be a relation between the amount of shivering and the incidence of ventricular fibrillation. In my first sixty patients receiving hypothermia where shivering was poorly controlled, I encountered four cases of ventricular fibrillation. All patients were revived and are well, but since I have carefully avoided producing shivering in patients since that time and have kept temperatures above 28° C., spontaneous ventricular fibrillation has caused little concern.

In my laboratories an attempt was made to compare the relative effects of cyclopropane and pentobarbital on ventricular fibrillation.[17] The dogs asleep with pentobarbital did not fibrillate while some of those receiving cyclopropane did. However, shivering was not controlled and, since the animals receiving cyclopropane shivered more than those receiving pentobarbital, no definite conclusion can be drawn concerning the effects of the anesthetic agent per se.

Narcosis and Survival Time

Miller and his co-workers,[18] in the course of their study on anoxia and hypothermia, have obtained some data on anesthetic factors. In the conscious animal, reduction of core temperature was resisted by mechanisms that increased metabolism 200 to 400 per cent. They observed that cooling to 20° C. not only prolonged survival from asphyxia, but permitted recovery

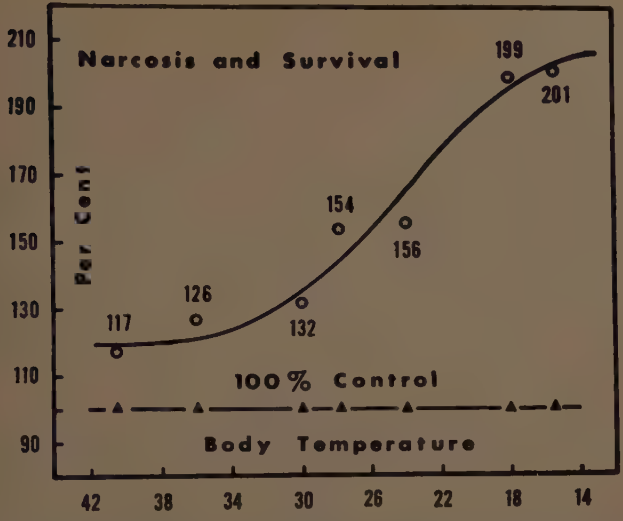

Figure 1. Effect of narcosis upon time of death of neonatal guinea pigs at seven different body temperatures. Results are graphed as percentages of nonnarcotized littermate survival time. Reproduced by permission of The American Physiological Society.[18]

from exposures that were lethal to warmer littermates. Survival time of Nembutal-injected animals at 40° C. was increased to 117 per cent of that for the water-injected controls and to 194 per cent at 14° C., using neonatal guinea pigs. The last gasp of the animal was taken as a measure of time of death (figure 1). In a series of experiments to determine the effects of hypothermia, Nembutal, and hydrogen peroxide, several groups of littermates were used. One of each litter was a normothermic control, asphyxiated. The second received injections of water before asphyxia. The third was cooled and received hydrogen peroxide before the asphyxia. The fourth was cooled and received both Nembutal and hydrogen peroxide. Results show that Nembutal increased the survival time of the cooled peroxide-treated animals by 62 per cent over those that did not receive Nembutal

Table 1

Effects of Combining Hypothermia, Nembutal, and Hydrogen Peroxide*

	Percentages of control T.O.D.	Percentages of H_2O control T.O.D.	Percentages of hypothermic + peroxide T.O.D.
Control—normothermic	100		
Control—normothermic + H_2O	124	100	
Hypothermic + peroxide	329	265	100
Hypothermic + nembutal + peroxide	543	437	162

* Reproduced by permission of The American Physiological Society.[18]

(TABLE 1). The protective action of Nembutal in asphyxia, according to Miller, was largely due to the depression of metabolism that it produced, as measured by oxygen uptake.

Miller also carried out a series of similar experiments in which he used cessation of ventricular activity as seen on the electrocardiogram as a sign of death. Under these circumstances, the time of arrest after asphyxia was unaffected by Nembutal in either warm or cooled animals. The heart, therefore, seemed not to be benefited by sedation during asphyxia (TABLE 2).

TABLE 2
EFFECTS OF TEMPERATURE AND SEDATION ON TIME OF VENTRICULAR ARREST*

	Temperature (°C.)	Last gasp (sec.)	Ventricular arrest (sec.)
Normothermic	36.8	272.8	809
Sedated normothermic	37.3	530.5	940
Hypothermic	21.9	399.3	1570
Sedated hypothermic	20.1	674.5	1500

*Reproduced by permission of The American Physiological Society.[18]

Summary

The relationship of anesthesia to hypothermia may be better understood if the term anesthesia is divided into separate concepts. Incomplete anesthetic agents (pentobarbital, thiopental, procaine, ethanol, chlorpromazine, relaxing agents, urethans) fall short of causing loss of mental activity, reflex activity, sensory response, and motor activity. The complete anesthetics (ether, chloroform, cyclopropane) may destroy all four types of action. Induction of hypothermia per se is probably a stimulating event, and necessitates loss of motor and perhaps reflex activity. Anesthetic agents that inhibit these activities tend to enhance the lowered metabolism encountered in adequate hypothermia; incomplete anesthetic agents may permit the stimulus of applied hypothermia actually to increase metabolism.

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BIOCHEMICAL CHANGES IN HUMAN BEINGS DURING REFRIGERATION ANESTHESIA*

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Cardiac surgery with its protracted interruption of cardiac outflow offers an opportunity to study the human organism under severe conditions of ischemia. During ischemia metabolic activity continues anaerobically, resulting in marked alterations in the concentration of certain metabolites in the tissue fluids. By catheterization of selected vessels it is possible to investigate the course of events in an organ almost as if it were studied under isolated conditions. We shall describe certain phenomena that have been observed in the metabolism of lactate and bicarbonate as they affect the *p*H of the blood, in order that some insight may be gained into the mechanism of irreversible damage caused by ischemia.

After the circulation to the brain and peripheral tissues has been interrupted for prolonged periods, the composition of the first blood to flow through these tissues upon release of the occlusion should be a reflection of the changes that have occurred in the intracellular fluids. This is similar to the stop-flow technique that has been applied to the study of renal physiology.[1] In this manner it has been possible to identify certain of the changes seen in the arterial blood with their site of origin. Measurement of arterial blood does not give a reflection of the severe changes that occur within the tissues, because arterial blood represents a considerable dilution. If a very pronounced change were to occur in only one organ, analysis of the mixed arterial blood would not reveal this change except, perhaps, as a minor variation. The first venous blood flowing through the organ should, however, show this in considerable detail.

These studies have been made on human beings undergoing cardiac surgery during hypothermia. The hypothermia was preceded by preliminary medication with barbiturate and with curare or similar blocking agent. The barbiturate dosage was very small, and it is assumed that the effects of barbiturate were insignificant in respect to the total picture observed during the course of the hypothermia. Patients were prepared prior to hypothermia with catheters in the femoral artery and iliac vein. In the case of the iliac vein, the catheter was inserted to approximately the bifurcation of the vena cava, and care was taken that the catheter would not lie above the orifices of the renal veins. When the chest was opened, a catheter was threaded through the superior vena cava into the jugular bulb for the cerebral venous samples. Measurements of oxygen saturation, hemoglobin, hematocrit, *p*H, bicarbonate content, lactic acid, urea, ammonia, and glucose were made

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throughout the operation on all of the blood samples taken. Samples were taken before the initiation of hypothermia, during the development of hypothermia, immediately prior to the occlusion of the cardiac vessels, and immediately after the release of the occlusion of the cardiac vessels. Following the release of the occlusion of the cardiac vessels, 1-minute, 3-minute, and 5-minute samples were taken of the washout blood. Further determinations were made throughout the rest of the operative procedure until the patient was taken from the operating room. In some cases observations were made, after the recovery, at the bedside. Certain cases underwent 2 occlusions, and appropriate observations were made during the course of these procedures. The complete occlusion of the circulation lasted from 3 to 14 minutes. Of the 6 cases upon which this report is based, 2 had 2 occlusions. One had an occlusion lasting 14 minutes, followed 30 minutes later by one lasting 10 minutes. Another had a first occlusion lasting 7 minutes, followed 7 minutes later by a second occlusion lasting 8 minutes. The chemical findings on the blood washed out from the muscle and brain in the patients with a single occlusion were the same as in the patients with the double occlusion. In this small series there is no evidence of a relation between the amount of deviation of a postocclusion observation from the normal range and the duration, individual or total, of occlusion.

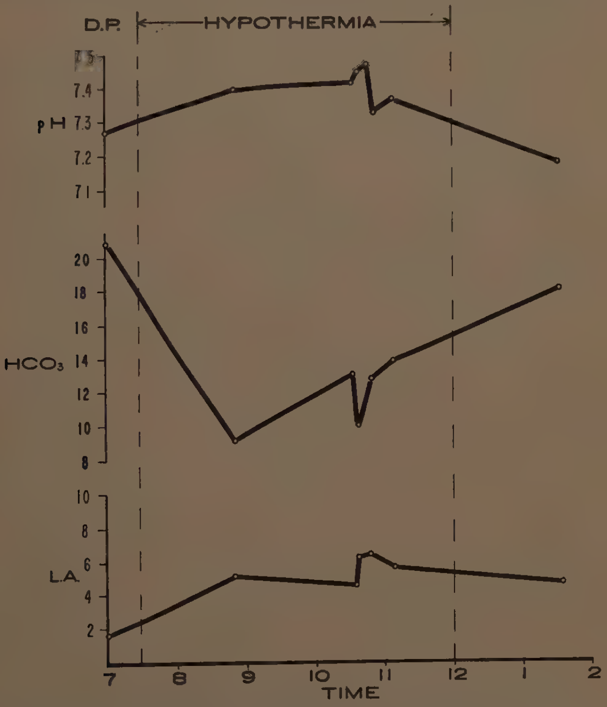

FIGURE 1. Venous *p*H, bicarbonate, and lactic acid during hypothermia and cardiac surgery. Temperature, 26.5° C.; total occlusion 10:37 to 10:48 A.M.

Results

FIGURE 1 shows a set of values for venous *p*H, bicarbonate, and lactic acid during the course of hypothermia, in an operation lasting for approximately 6 hours. The values for lactic acid and bicarbonate are expressed in mEq./l. During the course of hypothermia the *p*H of the blood was maintained fairly constant even though there was a sharp drop in the bicarbonate content, which was not equivalent to the rise in the lactic acid level. In fact, the rise in lactic acid can account for only about one third of the drop in bicarbonate, and the return of these values for bicarbonate to normal from the first drop to which they fell during the early part of hypothermia also was not accompanied by an alteration in lactic acid. This we found uniformly to be the case in the large, long-term fluctuation that occurred in all of our patients. On the other hand, during the course of the occlusion that occurred at 10:30 and lasted for 11 minutes, it can be seen that the alteration in bicarbonate did correspond, to a certain degree, with the fluctuation in lactic acid, and was related approximately quantitatively. The venous *p*H was similarly related, but the long-term fluctuation in bicarbonate again did not relate to

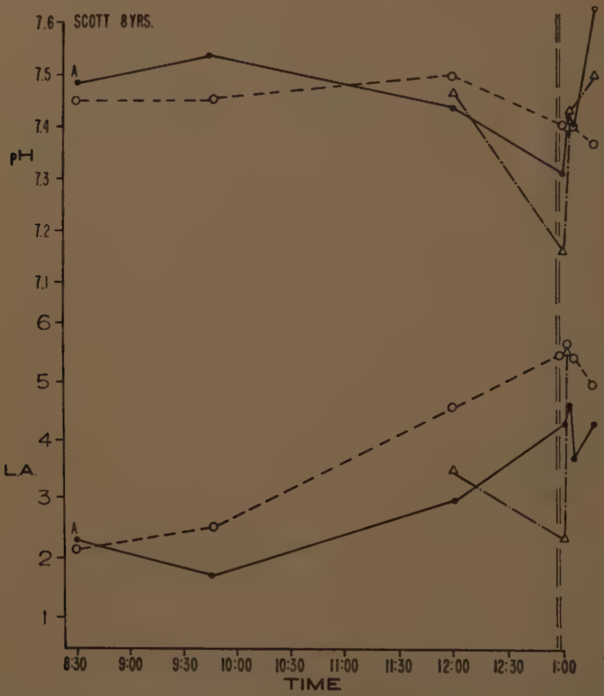

FIGURE 2. Arterial (*solid line*), venous (*dashed line*), and jugular bulb (*interrupted line*), curves for *p*H and lactic acid (mEq./l.). Total occlusion, 12:52 to 1:00 P.M.; hypothermia, 28 to 29.5° from 9:45 to 1:45 P.M. Bicarbonate values (A-V-J) were, 12:00: 29, 37, and 38; 1:01: 35, 34, and 49; 1:06: 32, 34, 32 mEq./l.

the venous pH during the latter part of the operation following occlusion. As the pH dropped, the bicarbonate level rose, which shows the independence of these 2 parameters in this situation.

FIGURE 2 shows the variations in pH and lactic acid during the course of another case. The hypothermia began at 9:00 A.M. The initial values for pH were relatively normal, and this case shows the small rise seen in arterial pH during the initiation of hypothermia in all of our cases. The value for jugular pH fell between the values for arterial and venous pH at the same time. The lactic acid rose slowly during the course of hypothermia, and showed no marked fluctuation in the venous and arterial values, although it is quite clear that the origin of the lactic acid rise is peripheral, for the venous level exceeds the arterial level by a considerable amount. The initial fall, during occlusion, of jugular lactic acid, however, suggests that there was uptake of lactic acid by the cerebral tissues, which stopped and became an excretion or loss of lactic acid shortly after the occlusion was released. This peculiar variation in lactic acid was completely unrelated to the fluctuation in pH of the cerebral blood, for the first washout blood showed the usual marked drop in pH seen in the cerebral vessels of all of our cases. In this

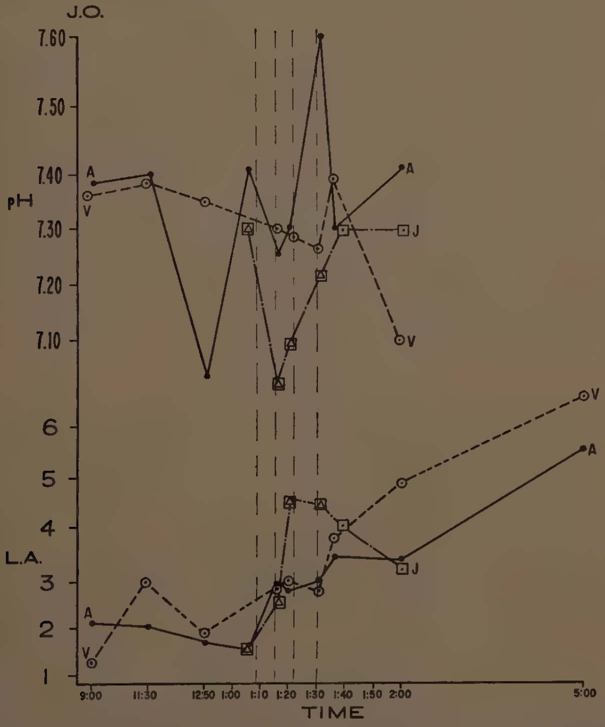

FIGURE 3. Arterial (*solid line*), venous (*dashed line*), and jugular bulb pH and lactic acid values during hypothermia with two periods of total occlusion: 1:08 to 1:15 P.M. and 1:22 to 1:30 P.M. Hypothermia, 30° C., 11 A.M. to 2 P.M.

case the pH went to 7.15, yet at the same time the lactic acid had fallen lower than the resting value, so that the drop in pH during hypothermia could not have taken place because of increase of lactic acid in the cerebral tissues. FIGURE 3 illustrates the unreliability of the arterial pH as an indicator of events in the tissues, for there was marked oscillation of the arterial pH, which was related to the efficiency of ventilation of the pulmonary blood, whereas the venous pH remained stable. On release of the occlusion, the highly ventilated pulmonary blood that remained in the lung during the occlusion showed a greatly elevated pH compared to the unventilated washout venous blood from the extremities. The pH of the first blood leaving the brain after occlusion is seen to be 7.00. The second occlusion in this patient did not produce a further drop in pH of the cerebral blood. The drop in cerebral pH was again unrelated to the minimal accumulation of lactic acid in the cerebral tissues shown during the first occlusion from 1:10 to 1:20 P.M. The greatest rise in lactic acid in the cerebral tissues occurred during the recovery from the first occlusion. This was accompanied by a rise in pH of the cerebral blood, rather than the fall in pH that should have occurred had the pH depended upon the lactic acid concentration as it affected the bicarbonate level. The pH change in the brain was due mainly to a rise in P_{CO_2}.

Discussion

Certain generalizations can be made about the changes in pH occurring during hypothermia and during the course of occlusion of the circulation. The arterial pH is much more variable than venous pH, and is a reflection of respiratory activity. Venous pH is usually lower than arterial, and usually is related inversely to the lactic acid level of the blood. Venous pH remains rather stable during refrigeration, but falls gradually during rewarming. The jugular pH falls very sharply during occlusion of the circulation, and can be shown to reach levels that have been considered as seriously dangerous to life at a time when the venous and arterial pH values have not changed markedly. Alterations in lactic acid, although pronounced, are usually not sufficient to account for the alterations in pH of blood taken from various sites. Some cases show an uptake of lactic acid by the brain during occlusion. This utilization may be merely a movement of lactic acid into the tissue with a subsequent loss of lactic acid from the tissue when oxygenation is reinitiated. All cases showed a considerable rise in arterial lactic acid, from two to three times the resting value, by the end of the operation. In some cases this rise appeared during the initiation of hypothermia and, in others, the most marked rise appeared during the rewarming. The data show that this alteration in lactic acid originates from the periphery, and the very marked rises that occur during occlusion of the circulation and following shortly after occlusion are the result of the inability of the organism temporarily to remove lactic acid, probably due to some degree of liver "failure."

The most striking change observed in this series, and the one that has the most apparent significance, is the severe acidosis that appeared in the cerebral tissues during the period of occlusion. Since this is an acidosis resulting from an increase P_{CO_2}, it is interesting to speculate upon the possible source of this great excess of CO_2. There is not a concomitant increase in lactic acid, which would be the case were this acidosis due to the accumulation of lactate resulting from anaerobic glycolysis; furthermore, there is little substrate for glycolysis available during complete occlusion. One possibility is the decarboxylation of glutamic acid to form γ-aminobutyric acid and CO_2, according[2] to EQUATION 1.

$$\text{Na glutamate} \rightarrow \gamma\text{-aminobutyric acid} + CO_2 + Na^+ \qquad (1)$$

There is sufficient glutamate in brain[3] to provide a quantity equivalent to 10 mM/l. of CO_2; γ-aminobutyric acid, the product, is amphoteric and would not affect the *p*H of the blood, but the reaction would consume 1 proton and liberate a positive ion. This would have a tendency to produce a bicarbonate alkalosis, rather than the high P_{CO_2} acidosis observed. In fact, except for 3 reactions, decarboxylation of oxalacetic acid, decarboxylation of oxalsuccinic acid, and the aforementioned glutamic decarboxylation, there are no known reactions in brain that could furnish quantities of CO_2 sufficient to cause a CO_2 acidosis. The recently discovered amino acid decarboxylations in brain,[4] although quite active, have such infinitesimal amounts of substrate available that the CO_2 to be produced from them would be quantitatively insignificant. The oxidative formation of carbon dioxide depends upon the presence of a reducible acceptor. Normally this is oxygen, according to EQUATION 2, for example, using succinate as substrate:

$$2\ Na_2\ \text{succinate} + O_2 \rightarrow 2\ Na_2\ \text{fumarate} + 2\ H_2O \qquad (2)$$

When the cerebral vessels are occluded, this source is abruptly shut off and acid production can proceed only by dismutative type of metabolism such as shown in EQUATION 3, in which pyruvate becomes the acceptor for hydrogen:

$$\text{Na pyruvate} + Na_2\ \text{succinate} \rightarrow \text{Na lactate} + Na_2\ \text{fumarate} \qquad (3)$$

The supply of pyruvate should be fairly limited, however, in view of the fact that there is little available carbohydrate in brain. One possible source of the acidosis is the deamidation of glutamine by the enzyme, glutaminase, which is present in large quantities in the cerebral tissues. There is sufficient glutamine,[3] EQUATION 4, to furnish 5 mM/l. of acid in this manner:

$$\text{glutamine} + \text{HOH} \rightarrow \text{glutamic acid} + NH_4^+ \qquad (4)$$

This reaction, however, would liberate the equivalent amount of ammonia, and there is no evidence from our data that ammonia is evolved from the brain either immediately after occlusion or during the course of recovery from occlusion. Nucleic acid hydrolysis could liberate large amounts of acid groups and could account for the considerable acidosis observed. We plan to test whether this reaction occurs during the course of hypothermia.

We may conclude, therefore, that the observation that severe acidosis occurs in the cerebral tissue during occlusion of the circulation during hypothermia cannot be accounted for at the present time. Further studies are required to elucidate the substrate for this acidosis, and it well may be that the material that decomposes, liberating acid during occlusion of the cerebral circulation, is an integral structural element of brain. This may be the cause of the irreversible change observed after brief occlusion of the cerebral circulation at normal temperatures.

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SUMMARY OF PANEL DISCUSSION ON PHYSIOLOGY OF HYPOTHERMIA IN THE HUMAN

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The panel discussion closed the conference on which this monograph is based and had as its aim a discussion of the salient features of the physiological effects of hypothermia in the human as observed through the experiences of the panelists. I was moderator; the other members of the panel were F. John Lewis, Northwestern University School of Medicine, Chicago, Ill.; Wilfred G. Bigelow, University of Toronto Faculty of Medicine, Toronto, Canada; R. Adams Cowley, University of Maryland School of Medicine, Baltimore, Md.; Robert W. Virtue, University of Colorado School of Medicine, Denver, Colo.; and Will C. Sealy, Duke University School of Medicine, Durham, N. C. This report only indicates the salient points considered.

Lewis opened the discussion by presenting slides demonstrating a modified and highly simplified technique for vascular cooling, which permits alteration of deep body temperature more quickly than surface contact methods and also permits more adequate control at the desired level. Sealy discussed the heat transfer system that his group has been using with great success. He has been able to cool patients down to levels of 30° C. within 5 min., to maintain that temperature as required for the operative intervention, and then to rewarm the patients to normal body temperature with equal rapidity. The great advantage of this type of system is the tremendous saving of time, during which the patient is in deep anesthesia. The other members of the panel use the surface contact method, either tub cooling or a blanket with coils through which warm or cold water is circulated. With the latter method, large temperature gradients are developed between the core and superficial body temperatures whereas, with the former (blood stream) method, the heart is cooled first and remains cooler than the rest of the body. This was felt to be more ideal, since surgery was directed primarily at the heart and this was the organ for which maximal protection is desired. Cowley agreed that this method was the most satisfactory, but he also stated that it was his impression that the brain was more important than the heart from the standpoint of protection during total circulatory arrest.

The subject of ventricular fibrillation compelled the greatest attention. Bigelow opened the discussion by stating that the single most important complication limiting the usefulness of hypothermia was this arrhythmia. As a result of clinical and experimental experiences, he now limits his levels of cooling to 30° C. for pure pulmonary stenosis and not below 28° C. for interatrial septal defects. At the former temperature safe total occlusion would be effected for 5 min. and, at the latter level, 8 min. Lewis and Virtue were in agreement with this; currently in their respective centers patients are never cooled below 28° C. Disagreement with these limitations was voiced by Cowley, who continues to cool patients to levels of 25 to 26° C. Cowley agreed that the incidence of ventricular fibrillation was higher below 28° C., but felt that the great advantage of prolonged circulatory arrest was too stringently compromised. Again he reiterated the need for protection of the brain and felt that deeper levels of hypothermia were indicated. Moreover, he maintains total circulatory arrest for an average of 15 min. at these low levels with no untoward consequences.

Sealy stressed the desirability of preventing ventricular fibrillation, not only with the limitation of hypothermia to the more moderate levels, but also with the use of prophylactic antifibrillatory drugs. He uses a mixture of magnesium sulfate, Prostigmin, and potassium injected via the coronaries, and has observed a marked reduction in incidence of ventricular arrhythmias, both experimentally and clinically. Virtue and Bigelow concurred with this, but use only Prostigmin with gratifying results. Cowley, on the other hand, uses no prophylactic agent. He notes that ventricular fibrillation occurs with regularity during surgery of the heart under hypothermia, but he controls the fibrillation with cardiac massage, administration of epinephrine, and electric defibrillation.

Bigelow brought up the subject of rewarm shock, manifested by hypotension, metabolic acidosis and/or respiratory acidosis, and low cardiac output. To a great extent he felt this was the result of the type of anesthesia used during the induction of the cooled state. At the present time, ether-oxygen anesthesia was felt to be the most desirable procedure to circumvent this rewarm shock state. The other participants, although they observed acidosis frequently, were not certain that an actual shock state is seen. It was felt that many circumventing factors, such as blood loss, may complicate the picture. I stated that experimentally this rewarm shock state was observed and was found to be due to an acute peripheral vascular insufficiency correctable by the administration of norepinephrine. In connection with the problem of acidosis, Virtue stated that the Colorado group hyperventilate the patients to keep them in a moderate degree of alkalosis to obviate the acidosis that precipitously appears during the latter part of the total circulatory occlusion and immediately after it. Lewis, on the other hand, administers 5 per cent CO_2 during hypothermia and attempts to maintain a normal *p*H, feeling that the important thing is to maintain a steady level of H-ion concentration and to prevent any sudden changes.

Sealy discussed his use of hypothermia in conjunction with pump-oxygenator systems. In this way the advantages of hypothermia are available as well as that of total bypass, essentially providing for longer periods of time for work on the open heart. Sealy employs only a moderate level of hypothermia (30° C.) and feels that this permits the use of lower flow rates, since blood flows at this hypothermic level are reduced. Cowley agreed with this in relation to more complicated defects. He still prefers hypothermia alone for the simpler defects. There appeared to be an increasing interest in the more rapid vascular cooling techniques such as the Duke University group uses.

Lewis mentioned the use of hypothermia for conditions other than cardiovascular surgery, citing its successful use in moribund patients with fulminating infections. This application of hypothermia has also been used in general surgery at the University of Maryland. Attention was then directed to the future probability of deeper levels of hypothermia in the human. Lewis and Bigelow have done experimental work cooling dogs to lower levels with successful resuscitation, and expressed the feeling that a human, in due course of time, could be cooled to deep levels around 18° to 20° C. The method to be used probably would be that of rapid blood stream cooling, as used presently by Sealy, with a view toward passing rapidly through the phase of myocardial excitability (28° to 24° C.) to near cessation of heartbeat. The advantage of this would be a marked increase in the safe period for surgery on the heart with maximal protection for the brain.

In summary, I concluded the panel discussion with the following statement: despite the fact that relatively little is known, or generally agreed upon, with regard to the physiological effects of hypothermia in the human, the technique has proved to be a valuable and safe tool in the treatment of disease in the human, especially in promoting the open approach to corrective heart surgery.

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